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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 08/823,999
Filing Date: March 25, 1997
Appellant(s): ROGERS ET AL.

Rivka D. Monheit
For Appellant

EXAMINER'S ANSWER

This is in response to the Substitute Appeal Brief filed 8/10/04.

The text of those sections of Title 35 U.S. Code not included in this appeal can be found in a previous Office Action herein.

(1) Real Party of Interest.

A statement identifying the real party of interest in contained in the Brief.

(2) Related Appeals and Interferences Identified.

A statement indicating that this application has previously been on appeal to the Board of Appeals as APPEAL NO: 2003-0074 is acknowledged.

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(3) Status of Claims.

The statement of the status of claims contained in the Brief is correct.

Claims 1-12 are pending.

Claims 7 and 9 have been withdrawn as directed to a non-election invention for the purposes of this appeal.

Claims 1-6, 8 and 10-12 are under consideration as the claims read on ant-Mac-1 (anti-CD11b/CD18) antibodies as the claimed "compound, which specifically inhibits or reduces leukocyte integrin-mediated adhesion of function in patients undergoing certain cardiovascular surgeries or procedures.

For clarity and in the interest of compact prosecution, the purpose of previously indicating that non-elected claims 7 and 9 were subject to the rejections under 35 USC 112, first paragraph, written description and enablement during prosecution was to put appellant on notice that these claims would be similarly rejected under 35USC 112, first paragraph,.

(4) Status of Amendments.

Appellant's statement of the status of amendments after final rejection contained in the Brief is correct.

The claims were last amended in the Amendment filed 1/30/04.

(5) Summary of Invention.

The summary of invention contained in the Brief is correct.

(6) Issues.

Appellant's statement of the issues in the Brief is correct with the exception of the following.

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Issues 1 and 2: For clarity and in the interest of compact prosecution, the purpose of previously indicating that non-elected claims 7 and 9 were subject to the rejections under 35 USC 112, first paragraph, written description and enablement during prosecution was to put appellant on notice that these claims would be similarly subject to these rejections under 35 USC 112, first paragraph, in the interest of compact prosecution.

Claims 7 and 9 have been withdrawn from consideration in the instant application.

Upon reconsideration, and in view of appellant's amended claims, the previous rejection under 35 USC 112, first paragraph, enablement with respect to claim 10 has been withdrawn.

Issue 3: The previous rejections under 35 USC 112, second paragraph, have been withdrawn in view of applicant's amended claims and upon reconsideration of metes and bounds of "stenosis" and "restenosis". See The Invention and Clarification of Terms in the Response to Argument below.

Upon the abandonment of USSN 09/776,533, the previous provisional rejection under the grounds of obvious double patenting has been withdrawn.

(7) Grouping of Claims.

Appellant's statement in the Brief that the claims must be separately assessed for patentability with respect to issues under 35 USC 112 and prior art is agreed with to the extent each claim must be considered on its own with respect to the statutes as well as the issues of record, which are set forth herein.

However, appellant's statement that the claim 10 and others recite limitations are not disclosed in the prior art is not agreed with because of the reasons of record and set forth herein wherein such claims are met under both 35 USC 102 and 103 for the reasons of record.

In addition, claims drawn to specific patient populations and treatment regimens (claims 3, 11, 12), pharmaceutically acceptable carriers (4) or antibodies as active compounds (claim 8) are rejected either as dependent claims of rejected claims under 35 USC 112, first paragraph, or as anticipated or obvious in view of the prior art for the reasons of record.

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Further, see CFR 1.192(c)(7) which states that merely pointing out differences in what the claims cover is not an argument as to why the claims are separately patentable.

For appeal purposes, it is deemed that the independent **claim 1 and dependent claims 2-5, 8 and 11-12** should stand or fall as they read on the scope of “compounds” under 35 USC 112, first paragraph, written description and enablement and as the prior art teach the elected species of antibodies that bind Mac-1 that read on the genus of compounds under 35 USC 102 / 103.

For appeal purposes, it is deemed that the independent **claim 6** stands rejected under **35 USC 112, first paragraph, written description and enablement**, as it reads on the scope of “compounds” “wherein the integrin is Mac-1 (CD11b/CD18)” other than “antibodies that bind Mac-1” (see claim 10).

For appeal purposes, it is deemed that the independent **claim 6 and dependent claim 10** stand rejection under **prior art** as it reads on the elected invention of “antibodies that bind Mac-1 (see claim 10)”.

(8) Claims Appealed.

The copy of the appealed claims contained in the Appendix to the **Substitute Appeal Brief**, filed 8/10/04, is correct.

(9) Art of Record.

The following is a listing of the art of record relied upon in the rejections of claims under appeal.

- A) Altieri et al., J. Biol. Chem. 268: 1847-1853 (1993).
- B) Anderson, Disease-a-Month 39(9): 617-670 (1993).
- C) Bendeck et al., J. Vasc. Res. 38: 590-599 (2001).
- D) Co et al., U.S. Patent No. 6,210,671.
- E) Coller et al., U.S. Patent No. 5,976,532.
- F) Dangas et al., Am Heart J. 132: 428-436 (1996).
- G) Diamond et al., J. Cell Biol. 130: 1473 - 1482 (1995).

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- H) Edgington, *Biotechnology* 20: 383-389 (1992).
- I) The ERASER Investigators, *Circulation* 100: 799-806 (1999).
- J) Fattori et al., *Lancet* 361: 247-249 (2003).
- K) Faxon et al., *J Am Coll Cardiol* 40: 1199-1204 (2002).
- L) Genetta et al., *Ann Pharmacol.* 30: 251-257 (1996).
- M) Hemker et al., *Emerging Drugs* 4: 175-195 (1999).
- N) Ikeda et al., *Am Heart J.* 128: 1091-1098 (1994).
- O) Inoue et al., *JACC* 28: 1127-1133 (1996).
- P) Kling et al., *Circulation Research* 77: 112-128 (1995).
- Q) Kling, *Arteriosclerosis and Thrombosis* 12: 997-1007 (1992).
- R) Kuntz, *Science* 257: 1078-1031 (1992).
- S) Mazzone et al., *Circulation* 88: 358-363 (1993).
- T) Pimanda et al., *Curr. Drug Targets Cardiovas. Haematol. Disord* 3 (2): 101-123 (2003).
- U) Rogers et al., *Circulation* 88: 1215-1221 (1993).
- V) Schwarz et al., *Thrombosis Research* 107: 121-128 (2002).
- W) Simon et al., *Circulation* 92, 8 Suppl: I-110, Abstract 0519 (1995).
- X) Simon et al., *Thromb. Vasc. Biol.* 17: 528-535 (1997).
- Y) Todd et al., U.S. Patent No. 4,935,234.
- Z) Topol et al., *JAMA* 278: 479-484 (1997) (cited by appellant).
- AA) Welt et al., *Arterioscler Thromb Vasc Biol* 22: 1769-1776 (2002).
- BB) Wu et al., *Thrombosis Research* 101: 127-138 (2001).

The following is a listing of art relied upon by appellant as Exhibits in addressing the rejections of record.

- CC) Coats et al., *Semin Interv Cardiol* 2: 153 – 158 (1997) (Exhibit).
- DD) Deitch et al., *Arterioscler Thromb Vasc Biol* 18: 1730-1737 (1998) (Exhibit).
- EE) Farb et al., *Circulation* 99: 44-52 (1999) (Exhibit).
- FF) Folts et al., *J Am Coll Cardiol* 33: 295-303 (1999) (Exhibit).
- GG) Kearney et al., *Circulation* 95: 1998-2002 (1997) (Exhibit).
- HH) Komatsu et al., *Circulation* 98: 224-233 (1998) (Exhibit).
- II) Mikelson et al., *J Am Coll Cardiol* 33: 97-106 (1999) (Exhibit).

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JJ) Rogers et al., *Circulation* 100 (Supp 1) (No. 18) : #1742, 11/2/99 (Exhibit).

KK) Simon et al., *J Clin Invest* 105: 293-300 (2000) (Exhibit).

LL) Topol et al., *JAMA* 278: 479-484 (1997) (Exhibit).

As indicated previously, the Board of Appeals has made the following of record (see Vacatur and Remand to the Examiner, mailed 9/3/03).

MM) Taber's Cyclopedic Medical Dictionary, 18th Ed., pages 130, 1666 and 1828 (1997).

(10) Grounds of Rejection.

Given the duplicate nature and number of the common evidentiary references in the rejections under 35 USC 112, first paragraph, written description and enablement, and under 35 USC 102; the examiner has set forth these rejections wherein such duplicative references are set forth in a different size font to decrease the length of the Examiner's Answer and to provide clarity in the interest of convenience for both appellant and the Board of Appeals.

The examiner apologizes for any inconvenience in this matter.

The following ground(s) of rejection are applicable to the appealed claims.

Rejection Under 35 U.S.C. 112, first paragraph, Written Description

Claims 1-6, 8 and 11-12 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

There is insufficient written description encompassing any "compound" which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function as well as "wherein the integrin is Mac-1 (CD11b/CD18) (see claim 6) in an amount effective to inhibit or reduce stenosis arising from coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissue or organs or restenosis

of a blood vessels following injury to vascular tissue” currently recited in the instant claims because the relevant identifying characteristics such as structure of other physical and/or chemical characteristics of the claimed “compounds” including “antibodies, molecules, peptides and peptidomimetics”, as currently claimed, or “ligands, proteins, antisense oligonucleotides and ribozymes”, as currently disclosed, encompass patentably distinct adhesion molecules (and pathways) and inhibitory compounds, wherein the compounds as well as the adhesion molecules differ in structure and modes of action (see Composition on pages 9-20 of the instant **specification**). The “compounds” encompass distinct and diverse structures and do not encompass common structural elements essential to the common utility of “specifically inhibiting or reducing leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or restenosis in patients undergoing the cardiovascular surgeries and procedures encompassed by the claimed methods (e.g. injury arises from angioplasty, atherectomy or endovascular stenting; see claim 3).

Appellant is relying upon certain biological activities and the disclosure of a limited representative number of species of “compounds which specifically inhibit or reduce leukocyte integrin-mediated adhesion or function” such as the exemplified anti-Mac-1 antibodies in an experimental animal model (see pages 22-23 of the instant **specification**) to support an entire genus of diverse and unrelated molecules and adhesion pathways. The instant invention encompasses any “compound” or antagonist that results in the desired binding and inhibitory effect on an the integrin or ligand selected from the group consisting of Mac-1 (CD11b/CD18), LFA-1 (CD11a/CD18), p150,95 (CD11c/CD18) and CD11d/CD18, yet the instant specification does not provide sufficient written description as to the identifying structural features of said “compounds” and the correlation between the chemical structure and the desired binding and inhibitory function.

The reliance on the disclosed limited number of known adhesion molecules or adhesion molecule-specific antibodies does not support the written description of any “compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function”, including any “antibody, molecule, peptide or peptidomimetic”. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biological or pharmacological activities. Therefore, structurally unrelated binding antagonists encompassed by the claimed “compounds” other than certain adhesion molecules or adhesion molecule-specific antibodies would be expected to have greater differences in their activities. “Compounds” encompassing “antibodies, ligands,

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proteins, nucleic acid regulators, antisense oligonucleotides, ribozymes and peptidomimetics” rely upon a myriad of distinct and diverse structures and do not encompass common structural elements essential to the common utility of “specifically inhibiting or reducing leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or restenosis” in patients undergoing cardiovascular surgeries and procedures.

Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required.

Hemker et al. (Emerging Drugs 4: 175-195, 1999) disclose that the hemostatic-thrombotic system is a non-linear system containing a number of nested positive and negative feedback loops and that at the present state of knowledge it is impossible to predict the effect of inhibition of a single reaction on the response of the complete system. For this reason, one cannot predict the antithrombotic potency of a compound from its biochemical properties. See entire document, including Summary on page 175.

In addressing the issue of restenosis with emerging therapies in cardiology and haematology, **Pimanda et al. (Curr. Drug Targets Cardiovas. Haematol. Disord 3 (2): 101-123, 2003)** discloses that from the 1980's to the present numerous drugs tested in animal models - particularly the pig - have suggested benefit, although until recently none have shown benefit in humans (see entire document, including Strategies to Reduce Restenosis on pages 101-102, overlapping paragraph). These authors conclude that “as the extent of the biological complexity of cell growth and regulation is understood, the unbridled enthusiasm at the dawn of the molecular era now has been tempered by a sense of reality. From the current evidence, it is likely that many drugs under development that target a particular molecular defect may prove ineffective alone and will probably need to be used in combination with cytotoxics in current use to achieve disease remission. (see the first paragraph of the Conclusion on page 117).

Fattori et al. (Lancet 361: 247-249, 2003) notes that “many different biological mechanisms contribute to restenosis and drugs that target only one pathway for a restricted period may have limited value in a multifactorial process” (see Preventing Restenosis on page 247). “Experience with systemically administered drugs, such as antiplatelet agents, anticoagulants, calcium-channel blockers, angiotensin converting-enzyme inhibitors, cholesterol-lowering agents and antioxidants has proven almost universally negative.”

Welt et al. (Arterioscler Thromb Vasc Biol 22: 1769-1776, 2002) notes that “studies of restenosis are limited by the fact that direct tissue examination is only rarely possible” (see page 1769, column 2, paragraph). Here, the authors further acknowledge that “animal models are not perfect mirrors of human pathology, and as proof, there are numerous examples of therapies that are effective in animals but not in humans.” Therefore, animal studies are best used to answer specific biological questions that give insight into human disease rather than to provide exact surrogates of human pathology.” Also, see entire document, including Implications for Antirestenotic Therapies on pages 1772-1774.

Cited by appellant, it is noted that **Topol et al. (JAMA 278: 479-484, 1997)** notes that a large number of pharmacological agents have failed to reduce restenosis or improve long-term outcomes and the only large-scale trial that reported an effect was the 23% reduction in clinical recurrence at 6 months using abciximab, a monoclonal fragment directed against the $\beta 3$ integrin (see Introduction on page 479).

Appellant also acknowledges the differences between the attempts to go from the experimental models to the achieving clinical success in stating: “No pharmacologic agent has yet been shown to reduce restenosis in humans” (see page 2, paragraph 2 of the instant **specification**).

Others have relied upon the same or similar models as appellant’s single experimental model with similar positive results only to observe the lack of positive results or efficacy in human clinical trials.

It is noted that **page 23, paragraph 2 of the instant specification discloses:** “For reference, appellant’s reliance upon the profound inhibition of experimental restenosis by M1/70, equal to or greater than the inhibition achieved in this same animal model by “gold-standard” experimental antiproliferative agents such as heparin and others, discussed by **Rogers et al. (Circulation 88: 1215-1221, 1993).**”

Heparin can inhibit smooth muscle proliferation and does bind Mac-1 (Diamond et al., J. Cell Biol. 130: 1473 - 1482, 1995). Despite its well known use as an anticoagulant, heparin has failed to show beneficial effects on restenosis (**Dangas et al., Am Heart J. 132: 428-436, 1996, particularly page 431, column 1).**

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Further, it is noted that anti-CD18 antibodies (Mac-1 / CD11b/CD18) have different effects on leukocyte extravasation, smooth muscle migration, intimal thickening and infarct size depending on the system under observation.

For example, **Kling (Arteriosclerosis and Thrombosis 12: 997-1007, 1992)** disclose that smooth muscle cells moved into the intima despite complete blockage of neutrophils with the potent inhibitor of leukocyte adhesive functions anti-CD18 antibody in an experimental model (see entire document, including the Abstract).

Kling et al. (Circulation Research 77: 112- 128, 1995) discloses that an anti-CD18 antibody in combination with anti-VLA-4 antibody can block mononuclear leukocyte emigration, thereby reducing smooth muscle cell migration in an experimental animal model (see entire document, including the Abstract and Discussion).

However, **Faxon et al. (J Am Coll Cardiol 40: 1199-1204, 2002)** disclose that while experimental studies have demonstrated that the inhibition of CD11/CD18 has resulted in significant reduction of infarct size and improved endothelial function, coronary blood flow, and left ventricular hemodynamics (See Introduction), an antibody to CD11/CD18 did not reduce infarct size in patients who underwent primary angioplasty (see entire document, including the Abstract and Discussion). Similar results were observed in patients with acute myocardial infarction receiving thrombolysis (see page 1203, column 1, lines 2-8).

With respect to the breadth of "compounds", there is insufficient written description of the wide variety of distinct and diverse compounds (e.g. molecules, antisense oligonucleotides, nucleic acid regulators, molecules from a complex mixture of random molecules, natural products and synthetic chemical compounds) which do not share a common structure that contributes to a common ability either to inhibit integrin-mediated interactions or to inhibit stenosis / restenosis.

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For example, appellant relies upon

(a) random generation of integrin or integrin encoding sequence binding molecules (e.g. see pages 14-15 of the specification);

(b) computer modeling technology (e.g. see page 15, paragraph 1 of the specification); and

(c) theoretical calculations and empirical findings for providing guidance for the design of oligonucleotides to inhibit gene expression (e.g. see page 18, lines 25-28 of the specification).

In addition, appellant relies upon the statement that "assays for testing compounds for useful activity can be based solely on the interaction of the compound with in the protein (e.g. see page 14, paragraph 1 of the specification).

However, no written description of such inhibitory peptides (other than the fibrinogen fragment disclosed on page 13, paragraph 3 of the **specification**), peptidomimetics, molecules or oligonucleotides compounds is disclosed in the specification as filed.

The **specification** appears to disclose only one peptide, that is, a particular fibrinogen fragment which modifies fibrinogen to Mac-1 described by Altieri et al. *J. Biol. Chem.* 268: 1847-1853 (1993) (see page 12, paragraph 3 of the **specification**). As indicated above, the only observation provided by the specification as filed is the administration of the anti-Mac-1 antibody M1/70 in an experimental animal model (see pages 22-23 of the **specification**).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

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One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. There, the specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

There is insufficient written description of the claimed "compounds" broadly encompassed by the claimed invention. There is a lack of disclosure of sufficient relevant identifying characteristics coupled with a known or disclosed correlation between function and structure of the broadly diverse compounds employed in the claimed methods.

While the specification discloses a starting point for screening or testing for compounds that inhibit or reduce leukocyte integrin - ligand interactions, the instant disclosure does not set forth sufficient procedures that will necessarily lead to discovery for such a compound and it does not identify suitable members of compounds such as peptidomimetics, antisense oligonucleotides, nucleic acid regulators, molecules from a complex mixture of random molecules, natural products and synthetic chemical compounds to provide a sufficient number of species to support the claimed genus of "compounds".

The application does no more than describe the desired function of the claimed compounds broadly encompassed by the claimed invention and does not contain sufficient information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention.

The claimed methods depend upon finding "a compound that specifically inhibits or reduces leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or restenosis in patients undergoing cardiovascular surgery and procedures". Without such a compound, the skilled artisan cannot practice the claimed method of treatment. It means little to invent a method if one does not have possession of the compound(s) that is (are) essential to practice the method. Without possession

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of the compound(s), the claimed endpoints are illusory and there is no meaningful possession of the method.

Applicant has not provided sufficient written description of a "compound which specifically inhibit or reduce leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue" broadly encompassed by the claimed invention.

Appellant has been reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 1115).

Appellant has been directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. Also, see MPEP 2163.

Therefore as indicated previously, the elected invention of anti-Mac-1 antibodies (and given evidence, certain soluble adhesion molecules and adhesion molecule-specific antibodies as well as the fibrinogen peptide discussed above disclosed in the specification as filed), but not the full breadth of the claimed "compounds", meet the written description provision of 35 USC 112, first paragraph.

To date, appellant has not provided sufficient evidence to support the possession of a sufficient number of species, particularly as it reads on the breadth of compounds encompassed in the claimed methods to reduce or treat stenosis or restenosis, as currently recited.

Rather, appellant has continued to maintain that there is sufficient written description for the full scope of the compounds, including undescribed peptides, peptidomimetics and molecules employed in the claimed methods.

Rejection Under 35 U.S.C. 112, first paragraph, Enablement

Claims 1-6, 8 and 11-12 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs such as pharmacological compounds which inhibit stenosis or restenosis can be species- and model-dependent, it is not clear that reliance on the in vitro and in vivo evidence of inhibiting leukocyte-integrin-mediated adhesion with Mac-1-specific antibodies in an experimental model accurately reflects the relative efficacy of the claimed methods relying upon any "compound which specifically inhibits or reduces leukocyte-integrin-mediated adhesion or function" (e.g. compounds, molecules, peptides, peptidomimetics, anti-sense oligonucleotides, etc.; see pages 9-20 of the instant **specification** and instant **claims**) to inhibit or reduce stenosis or restenosis in patients undergoing certain cardiovascular surgeries or procedures.

Although the claims are read in the context of the anti-Mac-1 antibodies as the elected compound of the claimed invention; the following is noted as the claims read on "a compound which specifically inhibits or reduces leukocyte-integrin-mediated adhesion".

The claimed "compounds" encompass any compound, integrin, ligand, molecule, peptide or peptidomimetic or others disclosed on pages 9-20 of the instant **specification**, which are disclosed and asserted to be capable of inhibiting or reducing leukocyte-integrin-mediated adhesion to inhibit or reduce stenosis or restenosis. However, the claims do not recite sufficient structural elements or specificity for the "compounds" encompassed by the claimed methods. The specification does not provide sufficient guidance and direction to identify and to enable any "compound" which might inhibit or reduce leukocyte-integrin-mediated adhesion which inhibits or reduces stenosis or restenosis, including achieving these therapeutic endpoints in human patients in need thereof.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (**Edgington, Biotechnology 20: 383-389, 1992**; see entire document, particularly page 386, column 3, paragraph 4).

The success of state of the art structure-based strategies for inhibitor design is highly unpredictable. For example, **Kuntz, Science 257:1078-1031 (1992)**, particularly on page 1080, column 3, discloses that as little as 2% of compounds predicted to inhibit specific enzymatic or receptor systems actually show inhibition in the micromolar range. Kuntz further discloses that "optimization" of these compounds has proven even more problematic.

Hemker et al. (Emerging Drugs 4: 175-195, 1999) disclose that the hemostatic-thrombotic system is a non-linear system containing a number of nested positive and negative feedback loops and that at the present state of knowledge it is impossible to predict the effect of inhibition of a single reaction on the response of the complete system. For this reason, one cannot predict the antithrombotic potency of a compound from its biochemical properties. See entire document, including Summary on page 175.

In addressing the issue of restenosis with emerging therapies in cardiology and haematology, **Pimanda et al. (Curr. Drug Targets Cardiovas. Haematol. Disord 3 (2): 101-123, 2003)** disclose that "from the 1980's to the present numerous drugs tested in animal models - particularly the pig - have suggested benefit, although until recently none have shown benefit in humans" (see entire document, including Strategies to Reduce Restenosis on pages 101-102, overlapping paragraph). These authors conclude that "as the extent of the biological complexity of cell growth and regulation is understood, the unbridled enthusiasm at the dawn of the molecular era now has been tempered by a sense of reality. From the current evidence, it is likely that many drugs under development that target a particular molecular defect may prove ineffective alone and will probably need to be used in combination with cytotoxics in current use to achieve disease remission" (see the first paragraph of the Conclusion on page 117).

Fattori et al. (Lancet 361: 247-249, 2003) notes that "many different biological mechanisms contribute to restenosis and drugs that target only one pathway for a restricted period may have limited value in a multifactorial process" (see Preventing Restenosis on page 247). "Experience with systemically administered drugs, such as antiplatelet agents, anticoagulants, calcium-channel blockers,

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angiotensin converting-enzyme inhibitors, cholesterol-lowering agents and antioxidants has proven almost universally negative.”

Welt et al. (Arterioscler Thromb Vasc Biol 22: 1769-1776, 2002) notes that “studies of restenosis are limited by the fact that direct tissue examination is only rarely possible” (see page 1769, column 2, paragraph). Here, the authors further acknowledge that “animal models are not perfect mirrors of human pathology, and as proof, there are numerous examples of therapies that are effective in animals but not in humans. Therefore, animal studies are best used to answer specific biological questions that give insight into human disease rather than to provide exact surrogates of human pathology.” Also, see entire document, including Implications for Antirestenotic Therapies on pages 1772-1774.

Cited by appellant, it is noted that Topol et al. JAMA 278: 479-484 (1997), which notes that a large number of pharmacological agents have failed to reduce restenosis or improve long-term outcomes and the only large-scale trial that reported an effect was the 23% reduction in clinical recurrence at 6 months using abciximab, a monoclonal fragment directed against the β_3 integrin (see Introduction on page 479).

For examination purposes, it is noted that c7E3, abciximab and ReoPro are all drawn to essentially the same inhibitory anti-GPIIb/IIIa 7E3 antibody which crossreacts with both $\alpha_v\beta_3$ and Mac-1 and, in turn, has been considered enabled with respect to the instant claims and has been applied in the prior art rejections with respect to Simon et al., Genetta et al. and Coller et al.

Appellant also acknowledges the differences between the attempts to go from the experimental models to the achieving clinical success in stating: “No pharmacologic agent has yet been shown to reduce restenosis in humans” (see page 2, paragraph 2 of the instant **specification**).

Others have relied upon the same or similar models as appellant’s single experimental model with similar positive results only to observe the lack of positive results or efficacy in human clinical trials.

It is noted that page 23, paragraph 2 of the instant **specification** discloses: “For reference, appellant’s reliance upon the profound inhibition of experimental restenosis by M1/70, equal to or greater than the inhibition achieved in this same animal model by “gold-standard” experimental antiproliferative agents such as heparin and others, discussed by Rogers et al. (Circulation 88: 1215-1221, 1993).

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Heparin can inhibit smooth muscle proliferation and does bind Mac-1 (Diamond et al., J. Cell Biol. 130: 1473 - 1482, 1995). Despite its well known use as an anticoagulant, heparin has failed to show beneficial effects on restenosis (Dangas et al., Am Heart J. 132: 428-436, 1996, particularly page 431, column 1).

Further, it is noted that anti-CD18 antibodies have different effects on leukocyte extravasation, smooth muscle migration, intimal thickening and infarct size depending on the system under observation.

For example, Kling et al. (Arteriosclerosis and Thrombosis 12: 997-1007, 1992) disclose that smooth muscle cells moved into the intima despite complete blockage of neutrophils with the potent inhibitor of leukocyte adhesive functions anti-CD18 antibody in an experimental model (see entire document, including the Abstract).

Kling et al. (Circulation Research 77: 112- 128, 1995) disclose that an anti-CD18 antibody in combination with anti-VLA-4 antibody can block mononuclear leukocyte emigration, thereby reducing smooth muscle cell migration in an experimental animal model (see entire document, including the Abstract and Discussion).

However, Faxon et al. (J Am Coll Cardiol 40: 1199-1204, 2002) disclose that while experimental studies have demonstrated that the inhibition of CD11/CD18 has resulted in significant reduction of infarct size and improved endothelial function, coronary blood flow, and left ventricular hemodynamics (See Introduction), an antibody to CD11/CD18 did not reduce infarct size in patients who underwent primary angioplasty (see entire document, including the Abstract and Discussion). Similar results were observed in patients with acute myocardial infarction receiving thrombolysis (see page 1203, column 1, lines 2-8).

The instant **specification** relies upon screening for peptide and peptidomimetics compounds (pages 11-13) as well as screening for antisense oligonucleotides, nucleic acid regulators, molecules from a complex mixture of random molecules, natural products and synthetic chemical compounds (pages 13-19). The specification appears to disclose only one peptide, that is, a particular fibrinogen fragment which modifies fibrinogen to Mac-1 described by Altieri et al. J. Biol. Chem. 268: 1847-1853 (1993) (see page 12, paragraph 3 of the specification). As indicated above, the only observation provided by the

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specification as filed is the administration of the anti-Mac-1 antibody M1/70 in an experimental animal model.

The claims are not limited to the use of a single class of compounds but rather encompass a broad range of distinct compounds and specificities. The claimed methods encompass targeting a variety of integrin members (e.g. CD11a/CD18; CD11b/CD18; CD11c/CD18; CD11d/CD18) (or their ligands) and administering a variety of structural diverse compounds (e.g. antibodies, molecules, peptides, peptidomimetics, nucleic acid regulators, antisense oligonucleotides, ribozymes).

There is insufficient objective evidence that a single compound such as the M1/70 antibody in experimental models, as disclosed in the specification as filed, can be extrapolated to predict the efficacy of a myriad of diverse “compounds that inhibit or reduce leukocyte mediated adhesion or function” (e.g. molecules, peptides, peptidomimetics, oligonucleotides) in the claimed methods to inhibit or reduce stenosis or restenosis, commensurate in scope with the claimed invention.

Further, it appears that compounds that can bind Mac-1 such as heparin and anti-CD18 antibodies do not result in the inhibition of stenosis or restenosis in humans, despite success in various experimental model systems, including experimental model systems that mimic that relied upon for the anti-Mac-1 M1/70 antibody in the instant specification.

There is insufficient objective evidence that the skilled artisan would predict that such a diverse class of compounds specific for various targets would be recognized as a single class of compounds to reduce or inhibit stenosis or restenosis of a blood vessel following injury to vascular tissue.

Appellant is relying upon certain biological activities and the disclosure of a limited representative number of species such as anti-Mac-1 antibodies in an experimental model to support an entire genus of diverse and structurally unrelated compounds targeting a diverse adhesion molecules ligand-receptor molecules, interactions and functions. The instant invention encompasses any “compound which specifically reduces or inhibits leukocyte integrin-mediated adhesion or function” that results in the desired reduction or inhibition of stenosis or restenosis”, yet the instant specification does not provide sufficient guidance and direction as to the structural features of said “compounds” and the correlation between the chemical structure and the desired binding and inhibitory function. It has been well known

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that minor structural differences even among structurally related compounds or compositions can result in substantially different biological or pharmacological activities. Therefore, structurally unrelated binding antagonists encompassed by the claimed binding “compounds” would have been expected to have greater differences in their activities

The specification describes assays for determining whether a given compound has certain desired characteristics and identifies some broad categories of compounds that might work, this description of screening assays without more precise guidelines amount to little more than a starting point, a direction for further research.

The specification provides for a plan or an invitation for those of skill in the art to experiment practicing the claimed invention but does not provide sufficient guidance or specificity as to how to execute that plan. It provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement in that will enable any person skilled in the art to make and use the invention

The scope of the required enablement varies inversely with the degree of predictability involved and in cases involving unpredictable factors such as physiological activity more may be required. See MPEP 2164.03 and 2164.02.

Given the relatively incomplete understanding in the biotechnological field involved and the lack of a reasonable correlation between the narrow disclosure in the specification and broad scope of protection sought in the claims; the lack of enablement is deemed appropriate. See MPEP 2164.08.

In view of the lack of predictability of the art to which the invention pertains, methods of reducing or inhibiting stenosis or restenosis with a broad range of structurally diverse “compounds” to a variety of diverse specificities would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective therapies for inhibiting restenosis and stenosis, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a

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specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive for the breadth of "compounds" which specifically inhibits or reduces leukocyte-integrin-mediated adhesion that reduce or inhibit stenosis and restenosis in patients undergoing certain cardiovascular surgeries and procedures.

Rejection Under 35 U.S.C. 102(a)(b) Genetta et al.

Claims 1-6, 8, 10-12 stand rejected under 35 U.S.C. 102(a)(b) as being anticipated by **Genetta et al.** (*Ann Pharmacol.* 30: 251-257, 1996), as evidenced by **Schwarz et al.** (*Thrombosis Research* 107: 121-128, 2002), **Bendeck et al.** (*J Vasc Res* 38: 590-599, 2001), **Wu et al.** (*Thrombosis Research* 101: 127-138, 2001) and **The ERASER Investigators** (*Circulation* 100: 799-806, 1999).

Genetta et al. teach the results of clinical trials which have indicated that abciximab can reduce the incidence of abrupt closure and restenosis associated with PTCA performed in high risk patients, plays a role in the treatment of unstable angina and acute therapy of myocardial infarctions (see entire document, including Data Synthesis on page 251, column 1 and Clinical Trials on pages 253-254). It is noted that the patients were given bolus doses of 0.25 mg/kg antibodies prior to and after angioplasty (see pages 252-255).

Genetta et al. teach the mechanism of action of abciximab, including its ability to hinder platelets and fibrinogen from participating in platelet aggregation and to prevent von Willebrand factor binding (see page 252, column 2, Mechanism of Action).

However, **Genetta et al.** does not disclose the Mac-1-binding properties of abciximab.

Schwarz et al. describe the binding of abciximab to Mac-1, in particular the I-domain (also called A-domain) of the Mac-1 α subunit (see entire document, including the Abstract, Results and Discussion).

Schwarz et al. provide evidence that the GPIIb/IIIa-blocking antibody fragment abciximab could inhibit the binding of fibrinogen, iC3b and the coagulation factor X to Mac-1 and that the adhesion of the THP-1 cells to immobilized ICAM-1 and to fibrinogen was reduced significantly by abciximab (see entire document, including the Abstract).

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In determining the mechanisms of action by which the beneficial treatment with c7E3 (abciximab, ReoPro) has been associated with a reduction in coronary events and the need for revascularization, both **Bendeck et al.** and **Wu et al.** teach that the 7E3 antibody can reduce smooth muscle cell migration following vascular injury which resulted in a decrease in intimal size (see entire document, including Abstract and Discussion).

The **ERASER Investigators** note that potent platelet inhibition with abciximab does not reduce in-stent restenosis in their study (see entire document, including the Abstract). However, the reference notes that these results should not necessarily be extrapolated to balloon angioplasty because the mechanisms of restenosis differ (see page 805, paragraph 1).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods using abciximab in a number of thrombotic conditions, resulting in the inhibition or reduction of stenosis and/or restenosis. It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Also, see Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Thus, the clinical use and ability of abciximab to reduce the incidence of abrupt closure and restenosis associated with PTCA performed in high risk patients and to play a role in the treatment of unstable angina and acute therapy of myocardial infarctions anticipates the claimed methods in the absence of a manipulative difference between the prior art methods and the broadest reasonable interpretation of the instant methods.

It is noted that c7E3, abciximab and ReoPro are all drawn to essentially the same inhibitory anti-GPIIb/IIIa 7E3 antibody which crossreacts with both $\alpha_v\beta_3$ and Mac-1.

Rejection Under 35 U.S.C. 102(b) Simon et al. (1995)

Claims 1-6, 8 and 10 stand rejected under 35 U.S.C. 102(b) as being anticipated by **Simon et al. (Circulation 92, 8 Suppl: I-110, Abstract 0519, 1995)** as evidenced by **Schwarz et al. (Thrombosis**

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Research 107: 121-128, 2002), Bendeck et al. (J Vasc Res 38: 590-599, 2001), Wu et al. (Thrombosis Research 101: 127-138, 2001) and The ERASER Investigators (Circulation 100: 799-806, 1999).

Simon et al. teach that the 7E3 antibody is used to inhibit ischemic complications of coronary angioplasty and clinical restenosis and that this 7E3 antibody cross-reacts with Mac-1 (see Abstract).

Simon et al. teach the Mac-1-dependent adhesion to fibrinogen and ICAM-1 which are abundant in vessels walls and that Mac-1-expressing cells accumulate in restenosis lesions and have the potential to interact with other vascular cells by secreting growth factors and cytokines.

Schwarz et al. describe the binding of abciximab to Mac-1, in particular the I-domain (also called A-domain) of the Mac-1 α subunit (see entire document, including the Abstract, Results and Discussion).

Schwarz et al. provide evidence that the GPIIb/IIIa-blocking antibody fragment abciximab could inhibit the binding of fibrinogen, iC3b and the coagulation factor X to Mac-1 and that the adhesion of the THP-1 cells to immobilized ICAM-1 and to fibrinogen was reduced significantly by abciximab (see entire document, including the Abstract).

In determining the mechanisms of action by which the beneficial treatment with c7E3 (abciximab, ReoPro) has been associated with a reduction in coronary events and the need for revascularization, **Bendeck et al.** and **Wu et al.** teach that the 7E3 antibody can reduce smooth muscle cell migration following vascular injury which resulted in a decrease in intimal size (see entire documents, including Abstracts and Discussions).

The **ERASER Investigators** note that potent platelet inhibition with abciximab does not reduce in-stent restenosis in their study (see entire document, including the Abstract). However, the reference notes that these results should not necessarily be extrapolated to balloon angioplasty because the mechanisms of restenosis differ (see page 805, paragraph 1).

Appellant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods using 7E3 antibodies. It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Also, see Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Thus, the 7E3 antibody used to inhibit ischemic complications of coronary angioplasty and clinical restenosis anticipate the claimed methods in the absence of a manipulative difference between the prior art methods and the broadest reasonable interpretation of the instant methods.

It is noted that c7E3, abciximab and ReoPro are all drawn to essentially the same inhibitory anti-GPIIb/IIIa 7E3 antibody which crossreacts with both $\alpha_v\beta_3$ and Mac-1.

Rejection Under 35 U.S.C. 102(e) Coller et al.

Claims 1-6, 8, 10-12 stand rejected under 35 U.S.C. 102(e) as being anticipated by **Coller et al. (U.S. Patent No. 5,976,532)**, as evidenced by **Schwarz et al. (Thrombosis Research 107: 121-128, 2002)**, **Bendeck et al. (J Vasc Res 38: 590-599, 2001)**, **Wu et al. (Thrombosis Research 101: 127-138, 2001)** and **The ERASER Investigators (Circulation 100: 799-806, 1999)**.

Coller et al. teach the use of the 7E3 antibody to treat a number of thrombotic conditions, including providing 7E3 prior to angioplasty in effective amounts sufficient for inhibition of platelet aggregation as well as to prevent or reduce reocclusion that can occur after thrombolysis (see entire document, including Utility of Platelet-Specific Chimeric immunoglobulin in columns 5-7, Examples and Claims). Here, **Coller et al.** also teach that effective amounts can be given parenterally in pharmaceutical acceptable vehicles encompassed by the claimed limitations by administering the antibody before, alone with or subsequent to be administered with a thrombolytic agent or anticoagulant in amounts sufficient to prevent platelet aggregation that can result in reocclusion (Utility of Platelet-specific Chimeric Immunoglobulin). Antibody was given in dosages from 0.10- 0.30 mg / kg (e.g. see Example 3 on columns 11-15). It is noted that the severity of stenosis was reduced as visualized by angiography as well as by increase in the flow velocity signal (e.g. Case Report on columns 29-30, including column 29, lines 64-67).

Coller et al. also teach that the antibodies can be used in a variety of situations including prevent thrombosis in a pulmonary embolism, transient ischemic attacks, deep vein thrombosis, coronary bypass surgery, surgery to insert a prosthetic vessel as well as angioplasty procedures encompassed by the claimed methods (see columns 5-6, overlapping paragraph).

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However, **Coller et al.** does not disclose the Mac-1-binding properties of the 7E3 antibody.

Schwarz et al. describe the binding of abciximab to Mac-1, in particular the I-domain (also called A-domain) of the Mac-1 α subunit (see entire document, including the Abstract, Results and Discussion).

Schwarz et al. provide evidence that the GPIIb/IIIa-blocking antibody fragment abciximab could inhibit the binding of fibrinogen, iC3b and the coagulation factor X to Mac-1 and that the adhesion of the THP-1 cells to immobilized ICAM-1 and to fibrinogen was reduced significantly by abciximab (see entire document, including the Abstract).

In determining the mechanisms of action by which the beneficial treatment with c7E3 (abciximab, ReoPro) has been associated with a reduction in coronary events and the need for revascularization, **Bendeck et al.** and **Wu et al.** teach that the 7E3 antibody can reduce smooth muscle cell migration following vascular injury which resulted in a decrease in intimal size (see entire documents, including Abstracts and Discussions).

The **ERASER Investigators** note that potent platelet inhibition with abciximab does not reduce in-stent restenosis in their study (see entire document, including the Abstract). However, the reference notes that these results should not necessarily be extrapolated to balloon angioplasty because the mechanisms of restenosis differ (see page 805, paragraph 1).

Appellant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods using 7E3 antibodies in a number of thrombotic conditions, resulting in the inhibition or reduction of stenosis and/or restenosis.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Also, see Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

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Thus, the 7E3 antibody used to inhibit ischemic complications of coronary angioplasty and clinical restenosis anticipate the claimed methods in the absence of a manipulative difference between the prior art methods and the broadest reasonable interpretation of the instant methods.

It is noted that c7E3, abciximab and ReoPro are all drawn to essentially the same inhibitory anti-GPIIb/IIIa 7E3 antibody which crossreacts with both $\alpha_v\beta_3$ and Mac-1.

Rejection Under 35 U.S.C. 102(e) Co et al.

Claims 1-6, 8, 10-12 stand rejected under 35 U.S.C. 102(e) as being anticipated by Co et al. (U.S. Patent No. 6,210,671) (see entire document).

Co et al. teach methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury in various modalities including cardiac surgery such as coronary artery bypass and elective angioplasty (columns 17-18, overlapping paragraph and column 18, paragraph 3-4) wherein the L-selectin-specific antibodies can be used in combination with other humanized or human antibodies reactive with CD11b (i.e. Mac-1) (column 18, paragraph 1). Co et al. teach that the antibodies can be administered before during or after the administration of thrombolytic agents or angioplasty, including doses of 0.01-10 mg/kg, 0.14-5 mg/kg and 0.3-3 mg/kg (column 18, paragraph 4). Co et al. teach administering the antibodies parenterally in pharmaceutical compositions along with suitable carriers encompassed by the claimed invention in effective amounts that would be known or apparent to the skilled artisan (column 20, paragraph 1-4).

It is noted that the claimed methods recite "comprising" which leaves the claim open for the inclusion of unspecified ingredients and method steps even in major amounts. See MPEP 2111.03.

Appellant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods encompassed by the referenced combination therapy including the use of anti-CD11b antibodies in methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury in various modalities

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including cardiac surgery such as coronary artery bypass and elective angioplasty resulting in the inhibition or reduction of stenosis and/or restenosis. Although the reference does not disclose the limitations of stenosis and restenosis per se, these claimed endpoints would be achieved by the administration of effective amounts (column 18, paragraph 4 and column 20, paragraphs 1-4 to column 21, paragraphs 1-2) of CD11b / Mac-1-specific antibodies in the same patient populations (e.g. columns 7-18, overlapping paragraph) targeted and encompassed by the claimed methods.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Also, see Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Rejection Under 35 U.S.C. 102(b) Todd et al.

Claims 1-6, 8, 10-12 stand rejected under 35 U.S.C. § 102(b) as being anticipated by **Todd et al. (U.S. Patent No. 4,935,234)** (see entire document).

Todd et al. teach methods of reducing tissue damage occurring at an inflammatory site in a host experiencing a phagocyte-mediated inflammatory conditions, including inflammation from myocardial infarction or ischemia-reperfusion injury and the insertion of balloon catheters in the circulatory system with CD11b- / Mac-1- specific antibodies (see entire document, including Claims). **Todd et al.** teach providing the CD11b-specific antibodies prior to intervention as well as in single or multiple doses to attenuate the inflammatory responses (see column 1, paragraph 2). **Todd et al.** exemplify 1 mg/kg dosing (e.g. see column 7, paragraph 1 and column 9, paragraph 1).

Todd et al. teach that myocardial ischemia results from occlusion, reperfusion in the presence of a critical stenosis or narrowing of a blood vessel (e.g. column 6, paragraph 4). One of ordinary skill in the art would have immediately envisaged that providing the anti-CD11b antibody in therapeutic methods would have encompassed providing the antibody in a pharmaceutical composition comprising at least a "solution" at the time the invention was made. One of ordinary skill in the art at the time the invention was made would have immediately envisaged that the referenced teaching the insertion of balloon catheters in the circulatory system would have referred to angioplasty at the time the invention was made.

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The claim language is a statement of purpose and intended result and does result in a manipulative difference in the method steps of the claims.

The statement of the intended result of administering those amounts does not change those amounts or otherwise limit the claim.

Although the reference does not disclose the limitation of restenosis per se, these claimed endpoints would be achieved by the administration of effective amounts (e.g. to attenuate inflammatory responses (see column 1, paragraph 2; 1 mg/kg in column 7, paragraph 2 and reduce tissue damage, to inhibit undesired neutrophil functions in column 10, paragraph 1) of CD11b / Mac-1-specific antibodies in the same patient populations (e.g. column 10, paragraph 1) targeted and encompassed by the claimed methods

Appellant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods encompassed by the referenced combination therapy including the use of anti-CD11b antibodies in methods of therapeutic treatment of ischemia-reperfusion injuries resulting in the inhibition or reduction of stenosis and/or restenosis.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Also, see Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Rejection Under 35 U.S.C. 103(a)

Claims 1-6, 8, 10-12 stand rejected under 35 U.S.C. 103(a) as being unpatentable **Co et al. (U.S. Patent No. 6,210,671) AND/OR Todd et al. (U.S. Patent No. 4,840,793)** in view of **Simon et al. (Circulation 92, 8 Suppl: I-110, Abstract 0519, 1995), Mazzone et al. (Circulation 88: 358-363, 1993, Ikeda et al. (Am Heart J. 128: 1091-1098, 1994), Inoue et al. JACC 28: 1127-1133 (1996) and Rogers et al. (Circulation 88: 1215-1221, 1993).**

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Co et al. teach methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury in various modalities including cardiac surgery such as coronary artery bypass and elective angioplasty (see entire document, including columns 17-18, overlapping paragraph and column 18, paragraph 3-4) wherein the L-selectin-specific antibodies can be used in combination with other humanized or human antibodies reactive with CD11b (i.e. Mac-1) (column 18, paragraph 1).

Co et al. teach that the antibodies can be administered before during or after the administration of thrombolytic agents or angioplasty, including doses of 0.01-10 mg/kg, 0.14-5 mg/kg and 0.3-3 mg/kg (column 18, paragraph 4).

Co et al. teach administering the antibodies parenterally in pharmaceutical compositions along with suitable carriers encompassed by the claimed invention in effective amounts that would be known or apparent to the skilled artisan (column 20, paragraph 1-4).

Although the reference does not disclose the limitations of stenosis and restenosis per se, these claimed endpoints would be expected, intrinsic or desired endpoints by administering effective amounts (column 18, paragraph 4 and column 20, paragraphs 1-4 to column 21, paragraphs 1-2) of CD11b / Mac-1-specific antibodies in the same patient populations (e.g. columns 17-18, overlapping paragraph) targeted and encompassed by the claimed methods. The referenced methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury in various modalities including cardiac surgery such as coronary artery bypass and elective angioplasty (columns 17-18, overlapping paragraph and column 18, paragraphs 3-4), the ordinary artisan would have had an expectation of success that anti-CD11b antibodies would have inhibited or reduced restenosis or stenosis arising from patients undergoing certain cardiovascular surgeries and procedures.

Co et al. also differs from the not disclosing the use of anti-CD11b antibodies in the absence of L-selectin-specific antibodies per se.

Todd et al. teach methods of reducing tissue damage occurring at an inflammatory site in a host experiencing a phagocyte-mediated inflammatory conditions, including inflammation from myocardial

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infarction or ischemia-reperfusion injury and the insertion of balloon catheters in the circulatory system with CD11b- / Mac-1- specific antibodies (see entire document, including Claims).

Todd et al. teach providing the CD11b-specific antibodies prior to intervention as well as in single or multiple doses to attenuate the inflammatory responses (see column 1, paragraph 2).

Todd et al. exemplify 1 mg/kg dosing (e.g. see column 7, paragraph 1 and column 9, paragraph 1).

Todd et al. teach that myocardial ischemic results from occlusion, reperfusion in the presence of a critical stenosis or narrowing of a blood vessel (e.g. column 6, paragraph 4).

One of ordinary skill in the art at the time the invention was made would have readily understood that the referenced teaching the insertion of balloon catheters in the circulatory system would have referred to angioplasty.

Although the reference does not disclose the limitation of restenosis per se, these claimed endpoints would have been expected or desired endpoints by administering effective amounts (e.g. to attenuate inflammatory responses (see column 1, paragraph 2; 1 mg/kg in column 7, paragraph 2 and reduce tissue damage, to inhibit undesired neutrophil functions in column 10, paragraph 1) of CD11b / Mac-1-specific antibodies in the same patient populations (e.g. column 10, paragraph 1) targeted and encompassed by the claimed methods.

Simon et al. teach that the 7E3 antibody is used to inhibit ischemic complications of coronary angioplasty and clinical restenosis and that this 7E3 antibody cross-reacts with Mac-1 (see Abstract).

Simon et al. teach the Mac-1-dependent adhesion to fibrinogen and ICAM-1, ligands which are abundant in vessels walls and that Mac-1-expressing cells accumulate in restenosis lesions and have the potential to interact with other vascular cells by secreting growth factors and cytokines.

Simon et al. teach that the cross-reactivity of c7E3 with Mac-1 may play an additional role in inducing passivity of the vessel wall.

Therefore, **Simon et al.** provides additional motivation to target Mac-1 in therapeutic interventions associated with the complications of angioplasty including restenosis.

The following references provide further support for targeting Mac-1 in the treatment of complications of angioplasty including restenosis.

Mazzone et al. teach the CD11b/CD18 plays a major role in the leukocyte adhesion process and can be upregulated severalfold in response to chemotactic factors (see Background). **Mazzone et al.** further teach that patients with unstable angina have an increased expression of granulocyte and monocyte

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CD11b/CD18, indicating that an inflammatory reaction takes place with their coronary tree. Activation of these leukocytes may induce coronary vasoconstriction, favor thrombotic processes, and further activate platelets, thus having potential implications on the pathogenesis of unstable coronary artery disease (see Conclusion). The Discussion provides a teaching of the importance of CD11/CD18 in tissue injury in vivo in a number of animal models, including that the addition of anti-CD18 antibodies can reduce tissue injury and mortality in ischemia reperfusion injury-induced shock and myocardial infarct size (see Discussion on page 360, column 1).

Ikeda et al. teach the surface expression of CD11b of neutrophils increased significantly after percutaneous transluminal coronary angioplasty (PTCA) (see entire document, including Abstract, Results and Discussion). **Ikeda et al.** teach anti-CD11b antibody inhibits several neutrophil functions, including the binding of C3bi-opsonized particles, adhesive interactions of neutrophils, spreading on vascular endothelium and chemotaxis (see Discussion, particularly page 1095, column 2). **Ikeda et al.** further teach that anti-CD11b antibodies significantly reduced neutrophil accumulation within the infarct area (see Discussion, particularly page 1095, column 2). With respect to restenosis, Ikeda et al. teach that neutrophil activation after PTCA in humans appears to play an important role in the initial step of inflammatory phase and then to trigger the pathophysiologic chain reaction eventually resulting in coronary restenosis (see Clinical Implications on page 1096-1097). **Ikeda et al.** note here that activated neutrophils can potentiate platelet activity, in turn, leading to vasoconstriction and proliferation of vascular smooth muscle.

Inoue et al. teach inflammatory stimuli within the coronary vessels associated with coronary angioplasty upregulate Mac-1 expression on the surface of PMNs and this process is more marked in patients who experience later restenosis (see entire document, including Conclusions). The activation of neutrophil adhesion molecule after PTCA has valued as a predictor of subsequent restenosis (see Conclusion). **Inoue et al.** teach that the same cytokines that stimulate the expression of leukocyte adhesion molecules, such as Mac-1 also stimulate smooth muscle cell proliferation.

Rogers et al. teach that the inhibition of neointimal hyperplasia and thrombosis depends on the type of vascular injury and the site of drug administration (see entire document, including Abstract and Discussion). Here, **Rogers et al.** teach different forms of injury may require different therapeutics and complication of arterial intervention such as excessive neointimal hyperplasia and thrombosis may

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demand alternative therapeutic regimens. Duration, dose, and site of delivery rather than frank resistance to therapy may explain why experimental effective antiproliferative and antithrombotic agents fail clinically.

Although certain references do not disclose the targeted endpoint of reducing or inhibiting stenosis or restenosis per se, it was clear that the references do teach targeting Mac-1 with effective amounts encompassed by the claimed invention (e.g. 0.25 mg/kg or more in single or multiple doses) in order to inhibit various inflammatory consequences of Mac-1 expressing cells in therapeutic regimens associated with stenosis or restenosis such as angioplasty or bypass surgery. In addition, the combined references do teach targeting either stenosis, restenosis or endpoints associated with stenosis or restenosis (occlusion, intimal hyperplasia). The claimed methods comprises the same steps, the same effective amounts and the same targeted patient populations as the prior art. In addition, **Rogers et al.** teach duration, dose, and site of delivery are important in achieving therapeutic endpoints aimed at limiting restenosis such as inhibiting intimal hyperplasia (see entire document). Given the well known complications of stenosis and restenosis associated with various procedures such as angioplasty or bypass surgery at the time the invention was made, one of ordinary skill in the art would have had an expectation of success that treating these conditions or procedures with effective amounts of anti-Mac-1 antibodies would have resulted in the inhibition or reduction of certain endpoints associated with stenosis or restenosis arising in patients undergoing certain cardiovascular surgeries and procedures.

The different references differ from the claimed methods by not disclosing all of the known targeted conditions complicated by stenosis or restenosis as recited in the instant claims.

Given the combined teachings which including teachings of administering antibodies that bind Mac-1 / CD11b/CD18 to treat or to prophylactically treat a number of thrombotic conditions such as angioplasty and bypass surgery encompassed by the claimed methods, one of ordinary skill in the art would have been motivated to apply anti-Mac-1 antibodies to inhibit or reduce stenosis or restenosis in these various modalities with an expectation of success at the time the invention was made. It was well known by the ordinary artisan at the time the invention was made that angioplasty, atherectomy endovascular stenting, coronary artery bypass surgery, peripheral bypass surgery or transplantation of cells, tissues or organs was complicated by stenosis or restenosis.

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Given the various targeted applications such as cardiac surgery (coronary artery bypass) and angioplasty as well as transplantation as taught by **Co et al.** (e.g. columns 17-18) and **Todd et al.** (e.g. Summary of the Invention and Detailed Description) as well as the conditions including restenosis as indicated in the secondary references, one of ordinary skill in the art would have targeted Mac-1 to inhibit the contribution of inflammatory cells such as neutrophils to the occlusion of blood vessels such as stenosis or restenosis in various conditions at the time the invention was made. Therefore, it would have been obvious to target those conditions recited in independent claims 1 and 6 at the time the invention was made.

Further, the composition forms set forth in claim 4 were well known and practiced at the time the invention was made. Also see columns 20-21 of **Co et al.** Note that **Rogers et al.** teach that duration, dose, and site of delivery were important in achieving therapeutic endpoints aimed at limiting restenosis such as inhibiting intimal hyperplasia.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(11) Response to Argument

A) The Invention and Clarification of Terms

Stenosis and Restenosis

1) As indicated previously, the Board of Appeals has made the following of record (see Vacatur and Remand to the Examiner, mailed 9/3/03).

Taber's Cyclopedic Medical Dictionary, 18th Ed., pages 130, 1666 and 1828 (1997) set forth the following definitions.

Stenosis: The constriction or narrowing of a passage or orifice.

Aortic Stenosis: Narrowing of the aorta or its orifice due to lesion of the wall with scar formation.

Restenosis: The recurrence of a stenotic condition as in a hear valve or vessel.

2) The following excerpt from Fattori et al. (*Lancet* 361: 247-249, 2003; see page 247-248, Mechanisms of Restenosis and Preventing Restenosis) has been set forth in the interest of setting some groundwork to the issues set forth in the instant application.

Mechanisms of Restenosis:

Restenosis is the reduction of the luminal size due to loss of gain in lumen size after intravascular interventional procedures. Several cellular and molecular events occur sequentially after a vascular injury. The initial response of the elastic fibers of the vascular wall to overstretching by balloon catheter is elastic recoil, response for the loss of gain, which characterises the early phase or restenosis. The endothelial denudation and the exposure of the subintimal components cause platelet adherence and aggregation, fibrinogen binding, and thrombus formation. Thrombus formation can also act as a scaffold into which vascular smooth muscle cells can migrate, synthesise matrix and collagen, and reorganise the thrombus, providing the substrate for neointimal formation. Activated platelets release several mitogens and chemotactic factors, which stimulate smooth muscle cell migration and proliferation into the injury site. Inflammatory mediators and cellular elements contribute to trigger a complex array of events that modulate matrix production and cellular proliferation. Finally, remodeling, a gradual dynamic process mediated by adventitial myofibroblasts that leads to a change in vessel size by constrictive remodeling without an overall change in tissue volume, contributes to the loss of lumen at later time. Stenting reduces elastic recoil and negative remodeling, the mechanical components of restenosis, but also stimulates the cellular mechanisms yielding to in-stent restenosis.

By contrast with balloon angioplasty, restenosis after stenting is due mostly to neointimal formation. The bulk of in-stent restenosis consists of extracellular matrix, proteoglycans, and collagen, with only 11% cells. Greater neointimal proliferation is associated with deeper medial penetration of stent struts, contradicting the idea that in percutaneous coronary intervention a larger lumen achieved by angioplasty diminishes the rate of restenosis. Moreover arterial medial disruption and lipid-core penetration by stent struts is associated with greater numbers of inflammatory cells by contrast with strut in contact with fibrous plaque, highlighting the role of inflammation in restenosis and its relation with the morphology of the atherosclerotic plaque.

Preventing Restenosis

Much research into many mechanical devices and drugs has been done to prevent restenosis, providing the rationale for an enormous number of clinical trials, but none have been proven to be effective. Many different biological mechanisms contribute to restenosis and drugs that target only one pathway for a restricted period may have limited value in a multifactorial process. Experience with systemically administered drugs, such as antiplatelet agents, anticoagulants, calcium-channel blockers, angiotensin-converting-enzyme inhibitors, cholesterol-lowering agents, and antioxidants has proven almost universally negative. These agents were previously tested in animal models and found to be beneficial. The lack of efficacy in human studies may be in part due to insufficient concentration of drug at the injury site or lack of chronic dosing. In general, although animal models provide new insight into the mechanism of restenosis, biological and mechanical differences meant that therapeutic success of anti-restenotic therapies was not achieved in human beings.

3) In response to clarifying the issues concerning the metes and bounds of the claimed invention, appellant has indicated the following in the **Substitute Brief**.

As presented in the Summary of the Invention of the **Substitute Brief** and in response to the previous rejection under 35 USC 112, second paragraph, appellant has noted the following concerning metes and bounds or scope of the claimed invention.

Appellant notes that the compositions described herein are used to inhibit undesired responses to vascular injury that includes hyperplasia of vascular smooth muscle cells which occurs in response to injury of blood vessels, for example as a result of angioplasty, atherectomy, endovascular stenting coronary or peripheral arterial bypass used to open a stenotic or occluded vessel of transplantation of cells, tissue or organs (see Summary of the Invention on pages 5-6 of the **Substitute Brief**). Vascular smooth muscle cell hyperplasia triggered by the injured vessel can result in stenosis or restenosis of the blood vessel. Restenosis is a complex phenomenon, involving numerous complex interactions.

The method by which stenosis / restenosis is reduced is by inhibiting or reducing integrin-mediated leukocyte adhesion (see The Claims are Definite on page 24, paragraph 1 of the **Substitute Brief**).

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An effective amount of the compound which inhibits or reduces stenosis / restenosis following injury to a vascular tissue is defined in the specification on pages 20-21 of the instant specification (see page 24, paragraph 2 of the **Substitute Brief**).

Appellant notes that: “The key parameter that is encompassed by the disorders recited in the claims is the involvement of leukocyte integrin-mediated adhesion, which, in turn, are targeted by inhibitor of leukocyte integrin-mediated adhesion (see page 25, paragraph 2 of the **Substitute Brief**). The claims are drawn to the use of inhibitors of leukocyte integrin-mediated adhesion, a readily measurable function.”

As page 25, paragraph 3 of the **Substitute Brief** continues: “The common feature between the disorders listed in claim 3 is the role of integrin-mediated leukocyte adhesion. Administering a compound to specifically inhibit / reduce integrin binding will be effect to treat, at least to some degree, all of these disorders. The effective amount can be routinely titrated for each patient depending on the compound and route of administration regardless of the disorder, to achieve therapeutic efficacy.”

Therefore, it appears that appellant and the examiner are on the same page in that the art recognized that several cellular and molecular events occur sequentially after a vascular injury and that inflammatory mediators and cellular elements contribute to trigger a complex array of events that modulate matrix production and cellular proliferation (e.g. see **Fattori** above).

Further, it appears that the appellant and the examiner are on the same page in that a compound such as an antibody (e.g. antibody that binds Mac-1 and inhibits Mac-1-mediated adhesion) which inhibits or reduces integrin-mediated leukocyte adhesion and is administered to a patient undergoing one of the claimed cardiovascular surgeries or procedures (e.g. bypass surgery, angioplasty, atherectomy or endovascular stenting) anticipates or renders obvious the claimed methods.

In response to the examiner's provision of **Fattori** above, appellant notes that while **Fattori (2003)** states that the mechanisms of restenosis differ between balloon and in-stent catheter injuries, both models share the feature of leukocyte integrin-mediated adhesion although to different degrees (see page 256, paragraph 3 of the **Substitute Brief**). Balloon catheter injury causes greater cell adherence than in-stent injury, which is consistent with Example 2 on pages 22-23 of the instant specification.

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This issue of distinguishing between balloon and in-stent catheter injuries was raised by appellant in the provision of the post-filing date reference to stand for the proposition that the 7E3 antibody (i.e. abciximab, Reopro) did not inhibit restenosis.

It is noted that Fattori does indicate differences between the balloon and in-stent injuries, which would explain the experimental results observed by submitted by appellant. Again, the prior art teachings provide for the use of the 7E3 antibody in balloon angioplasty. Appellant has not provide objective evidence to indicate that the 7E3 antibody failed to inhibit restenosis in these patients.

In addressing the issues below in the Section concerning (a) Animal Models are Predictive of Efficacy, appellant relies upon **Komatsu et al., Circulation 98 : 224-233 (1998)** that allegedly reports that animal models are generally predictive (page 230) with dogs being an exception (page 232). In describing the similarities and differences between experimental animal models and humans, **Komatsu et al.** suggest that it appears that the differences between restenosis and nonrestenosis are quantitative rather than qualitative (see page 232, column 2, lines 1-3).

This issue of quantitative versus qualitative distinctions in describing restenosis versus nonrestenosis would further suggest that administering an effective amount of a compound which inhibits or reduces leukocyte integrin-mediated adhesion or function, such as an antibody that binds and Mac-1-mediated interactions would have the inherent or expected property of inhibiting a patient in need, since the ordinary artisan would be administering the same compound (e.g. antibody that binds and inhibits Mac-1) to the same patient population (e.g. undergoing bypass, angioplasty, atherectomy or stenting) to achieve the same desired effect or the same underlying mechanism of leukocyte-mediated or Mac-1-mediated contributions to the complications associated with said patients in need.

Cited by appellant, it is noted that **Topol et al. JAMA 278: 479-484 (1997)**, which notes that a large number of pharmacological agents have failed to reduce restenosis or improve long-term outcomes and the only large-scale trial that reported an effect was the 23% reduction in clinical recurrence at 6 months using abciximab, a monoclonal fragment directed against the β_3 integrin (see Introduction on page 479).

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For examination and appeal purposes, it has been noted that c7E3, abciximab and ReoPro are all drawn to essentially the same inhibitory anti-GPIIb/IIIa 7E3 antibody which crossreacts with both $\alpha_v\beta_3$ and Mac-1 and, in turn, has been considered enabled with respect to the instant claims and has been applied in the prior art rejections with respect to **Simon et al.**, **Genetta et al.** and **Coller et al.**

Appellant's distinguishing restenosis from ischemia-reperfusion injury on page 12 of the Substitute Brief is acknowledged.

However, the examiner maintains the prior art teaches the administration of antibodies that bind and inhibit Mac-1-mediated interactions in the same patients in need undergoing the same cardiovascular surgeries and procedures to alleviate the same or nearly the same deleterious effects of said surgeries and procedures.

It is noted that the amended and currently pending claims more clearly recite the true nature of the claimed methods in that administering antibodies that bind and inhibit Mac-1 to cardiovascular patients in need would have the inherent or expected property of inhibiting or reducing stenosis or restenosis arising from the claimed surgeries or procedures.

On the record set forth in the instant prosecution and addressed in this Examiner's Answer, it is reasonable to conclude that the same patient is being administered the same active agent by the same mode of administration in the same amount in both the instant claims and the prior art references. Here, the stimulus or insult that leads to cellular and molecular events that occur sequentially after a vascular injury that is being targeted is the same or nearly the same cardiovascular surgeries or procedures between the prior art and the instant methods. The fact that appellant may have recited yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method. The claim language is only a statement of purpose and intended result. The expression does not result in a manipulative difference in the steps of the claims

4) Therefore, the issues are drawn to the following.

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Claims 1-6, 8, 11-12: For examination and appeal purposes, the rejections under 35 U.S.C. § 112, first paragraph, written description and enablement, are drawn to the recitation and scope of “compounds which specifically inhibit or reduce leukocyte integrin-mediated adhesion or function wherein the integrin is selected from the group consisting of Mac-1 (CD11b/CD18), LFA-1 (CD11a/CD18), p150,95 (CD11c/CD18) and CD11d/CD18 in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or restenosis in patients undergoing certain cardiovascular surgeries or procedures”, currently recited in the instant claims.

Claims 1-6, 8, 10-12: For examination and appeal purposes, the prior art rejections rely upon the administration of effective amounts of inhibitors of leukocyte integrin-mediated adhesion 1 (e.g. 0.25 mg/kg - 1.0 mg/kg), including antibodies that bind Mac-1 (CD11b/CD18) in patients undergoing angioplasty, atherectomy, endovascular stenting, coronary artery bypass surgery, peripheral bypass surgery or transplantation of cell, tissue or organs

As indicated above in (11)(A)(2)(3), appellant’s amendment of the claims as well as appellant’s comments concerning the metes and bounds of the claimed methods appear consistent with the prosecution by the examiner in this application.

However, appellant’s comments concerning that the claims are directed to methods of inhibiting or reducing accelerated arteriopathies such as stenosis arising from coronary artery bypass surgery, peripheral bypass surgery or transplantation of cells, tissue or organs or restenosis or a blood vessel following injury to a vascular tissue in a region of the blood vessel of a patient in need of treatment thereof (see pages 11-12 of the Substitute Brief) is somewhat misleading or confusing as “accelerated arteriopathies” is not a claimed feature, nor disclosed in the specification as filed.

Also for prior art purposes, given the current claim language, all that is required for the claims under art is to administer an inhibitor of leukocyte integrin-mediated adhesion, particularly an antibody that binds and inhibits Mac-1-mediated interactions as the elected invention, in effective amounts (e.g. 0.25 mg/kg - 1.0 mg/kg) in the patient populations recited in claims 1, 3 or 6 (e.g. undergoing bypass, angioplasty, atherectomy or stenting).

B) Rejection Under 35 U.S.C. 112, first paragraph, Enablement

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Appellant's arguments have been fully considered but are not found convincing essentially for the reasons of record.

Appellant asserts that the claims meet the legal standard for enablement by relying upon data in the application and subsequently showing the efficacy of two specific species of inhibitors, antibodies to Mac-1 (see pages 22-23 of the instant specification) and peptide inhibitors (see **Rogers et al., Circulation, 100 (Supp 1) (No. 18), 11/2/99, #1742; Exhibit**).

It is noted that the post-filing date **Rogers Circulation (1999) Abstract** describes:

that the site(s) of interaction between the urokinase receptor uPAR and Mac-1 is unknown and that they have identified a critical non-I domain binding site for uPAR on CD11b;

that the peptide M25 inhibited leukocyte adhesion to fibrinogen, vitronectin and cytokine-stimulated endothelial cells, even though it did not block ligand binding to Mac-1; and

that the M25 peptide is the first extracellular domain sequence of an integrin which broadly imparts integrin adhesion and migration to matrix proteins without directly inhibiting overall ligand binding, suggesting a novel strategy for regulation of integrin function in vascular injury and inflammation associated with atherosclerosis and restenosis.

Appellant has not provided a sufficient nexus or link between the post-filing identification of the M25 peptide to the instant specification. The instant **specification** does not disclose the M25 peptide, nor disclose the critical non-I domain binding site for uPAR on CD11b cited in the **1999 Abstract**.

While this **1999 Abstract** suggest the ability of this peptide in vascular injury associated with restenosis, the M25 peptide had not been tested in a manner that was reasonably predicted to inhibit or reduce stenosis or restenosis in patients in need undergoing the cardiovascular surgeries and procedures recited in the claimed methods.

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It is curious that appellant has relied upon the M25 peptide described in the post-filing date Rogers Circulation (1999) Abstract, while appellant has made no attempt to support the ability of the one disclosed fibrinogen peptide (see page 12, paragraph 3 of the specification) to achieve the in vivo characteristics required by the claimed methods.

In addition, appellant relies upon a lengthy discussion in the originally filed specification, that defines integrins and ligands (pages 7-10), classes of compounds, including antibodies (pages 9-10), peptides and peptidomimetics (page 11), methods for screening for compounds and generation of synthetic compounds randomly and by computer-aided design (pages 13-16) and nucleic acid molecules (pages 16-19).

Appellant asserts that the examiner has merely expressed the opinion that the claimed method is unpredictable and that no support for the lack of enablement is found in any of the Office Actions.

In contrast to appellant's assertions, appellant is invited to take time to read the rejections of record, which is reiterated above, for the objective evidence that supports the lack of predictability of the scope of "compounds" to reduce or treat stenosis or restenosis in patients undergoing cardiovascular surgeries or procedures.

While appellant relies upon years of efficacy following administration of antibodies and peptides, appellant has not addressed the facts placed in evidence to support the lack of predictability of the scope of "compounds" to reduce or inhibit stenosis or restenosis in patients undergoing cardiovascular surgeries or procedures, including human patients.

Appellant states: "It is ludicrous that they (appellants who are vascular surgeons) think the claimed method should work, while an examiner with no clinical training questions the results."

Given appellant's proposition, it would be reasonable to assume that rejections under 35 USC 112, first paragraph, should not be made in biotechnology patent applications, given that most, if not almost all, inventors filing biotechnology applications have an advanced degree (e.g. Ph.D. or M.D.) and represent institutions or companies that have experience in both experimental and clinical studies. Unless, of course, appellant's proposition is indicating that this dispensation should be granted only to the instant inventive entity or should be granted only to vascular surgeons.

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In either case, appellant's proposition runs contrary to patent practice and procedure as well as a long history of numerous legal decisions that have held the lack of compliance with 35 USC 112, first paragraph, by patents or patent applications with inventors who have such advanced degrees and experience.

Furthermore, appellant's proposition appears inconsistent with appellant's position throughout prosecution that has been made to cast dispersion on co-inventor's published work described in **Simon et al. (Circulation 92, 8 Suppl: I-110, Abstract 0519, 1995)**. Appellant has maintained that **Simon et al.** does not teach treating restenosis with an antibody that binds Mac-1 in contrast to clear and unambiguous statements in the reference to the contrary (see above). It appears that appellant is indicating that the inventive entity should be taken at their word without consideration or challenge in filing a broad disclosure in a patent application but should not be taken at their word when the same appellant (or co-inventor) publishes both experimental and clinical results for the public and ordinary artisans at the time the invention was made.

In addition, the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01(C).

(a) Animal Models are Predictive of Efficacy

Appellant notes that the rejection is based on the proposition that the animal models, specifically the rat and rabbit animal models used by appellant, do not correlate well with in vivo clinical trial results.

Appellant relies upon **Coats et al., Semin. Interv. Cardiol. 2: 153-158 (1997)** to note that animal studies in remodeling and its contribution to restenosis have been critical and correlated with human studies.

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It is noted that **Coats et al.** states: Evaluation of remodeling of the arterial wall following acute injury in experimental models has taken on substantial importance because of an increasing awareness that intimal hyperplasia may not necessarily be the most important pathophysiological component of restenosis following angioplasty (see Introduction on page 153 and Summary on page 157). The most promising model for studying the remodeling process which may mimic that found in man may be the non-human primate (see the last sentence of the Summary on page 157).

Appellant relies upon **Farb et al., Circulation 99: 44-52 (1999)** (see page 51, column 2) that states: "These data in the pig model regarding inflammation and thrombus closely reflect the findings observed in human coronary stenting early after implantation."

As appellant notes, these authors acknowledge differences in the types of injuries between animals and humans in response to atherosclerotic lesions.

Appellant relies upon **Komatsu et al., Circulation 98 : 224-233 (1998)** that allegedly reports that animal models are generally predictive (page 230) with dogs being an exception (page 232).

Komatsu et al. state that despite similarities between experimental animal models and humans, the present study also shows important differences in the healing phenomena after stenting (see page 230, column 1, paragraph 1).

It is noted that **Komatsu et al.** suggest that it appears that the differences between restenosis and nonrestenosis are quantitative rather than qualitative (see page 232, column 2, lines 1-3).

Appellant relies upon **Kearney et al., Circulation 95: 1998-2002 (1997)** which correlates results in humans obtained at autopsy with animal studies (bottom of page 1999, column 2).

Appellant relies upon **Folts, J. Am. Coll. Cardiol. 33: 295-303 (1999)** that notes that an animal model, the cyclic flow model of coronary thrombosis, has been useful in predicting which agents are likely to be of benefit in clinical trials.

Appellant asserts that the literature supports the use of animal models as predictive of efficacy.

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However, the rejection under 35 USC 112, first paragraph, enablement provides ample objective evidence to indicate that treating restenosis was unpredictable. See above for a complete analysis.

For example, in addressing the issue of restenosis with emerging therapies in cardiology and haematology, **Pimanda et al. (Curr. Drug Targets Cardiovas. Haematol. Disord 3 (2): 101-123, 2003)** disclose that “from the 1980's to the present numerous drugs tested in animal models - particularly the pig - have suggested benefit, although until recently none have shown benefit in humans” (see entire document, including Strategies to Reduce Restenosis on pages 101-102, overlapping paragraph).

Also, **Welt et al. (Arterioscler Thromb Vasc Biol 22: 1769-1776, 2002)** notes that “studies of restenosis are limited by the fact that direct tissue examination is only rarely possible” (see page 1769, column 2, paragraph). Here, the authors further acknowledge that “animal models are not perfect mirrors of human pathology, and as proof, there are numerous examples of therapies that are effective in animals but not in humans. Therefore, animal studies are best used to answer specific biological questions that give insight into human disease rather than to provide exact surrogates of human pathology.” Also, see entire document, including Implications for Antirestenotic Therapies on pages 1772-1774.

More importantly, the rejection has been made particularly in response to the scope of “compounds” and appellant’s limited disclosure to support the breadth of compounds employed in the claimed methods.

(b) Data Demonstrates Efficacy of Inhibiting Integrin-Mediated Inhibition

Appellant relies upon Example 2, on page 22 of the instant **specification**, showing administration of anti-Mac-1 to rabbits after arterial injury.

As indicated above, others have relied upon the same or similar models as appellant’s single experimental model with similar positive results only to observe the lack of positive results or efficacy in human clinical trials.

It is noted that **page 23, paragraph 2 of the instant specification** discloses: “For reference, appellant’s reliance upon the profound inhibition of experimental restenosis by M1/70, equal to or greater

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than the inhibition achieved in this same animal model by “gold-standard” experimental antiproliferative agents such as heparin and others, discussed by Rogers et al. (*Circulation* 88: 1215-1221, 1993).”

Heparin can inhibit smooth muscle proliferation and does bind Mac-1 (Diamond et al., J. Cell Biol. 130: 1473 - 1482, 1995). Despite its well known use as an anticoagulant, heparin has failed to show beneficial effects on restenosis (Dangas et al., Am Heart J. 132: 428-436, 1996, particularly page 431, column 1).

Therefore, it appears that the **specification** as filed relied upon the same or nearly the same “gold-standard” experimental model as employed for heparin and others, yet heparin and other agents have not been successful in inhibiting restenosis.

Again, it appears that appellant’s position is that when the experimental model shows positive results for one specific compound (anti-Mac-1 antibody) for appellant (e.g. pages 22-23 of the **specification**), then an entire genus of diverse “compounds” would be expected to be enabled, even though reliance upon the same or nearly the same model has not provided agents that treat restenosis.

Further, it has been noted that anti-CD18 antibodies (Mac-1 / CD11b/CD18) have different effects on leukocyte extravasation, smooth muscle migration, intimal thickening and infarct size depending on the system under observation.

For example, **Faxon et al. (J Am Coll Cardiol 40: 1199-1204, 2002)** disclose that while experimental studies have demonstrated that the inhibition of CD11/CD18 has resulted in significant reduction of infarct size and improved endothelial function, coronary blood flow, and left ventricular hemodynamics (See Introduction), an antibody to CD11/CD18 did not reduce infarct size in patients who underwent primary angioplasty (see entire document, including the Abstract and Discussion). Similar results were observed in patients with acute myocardial infarction receiving thrombolysis (see page 1203, column 1, lines 2-8).

Appellant relies upon **Simon et al., J. Clin. Invest. 105: 293-3000 (2000)**, which describes the role of inflammation in mechanical arterial injury, including Mac-1.

However, **Simon et al. (2000)** also states: “Although our data showing that antibody blockade of Mac-1 or absence of Mac-1 each reduce neointimal thickening after experimental angioplasty or endovascular stent implantation, the relevance of these observations to clinical angioplasty is unknown.” See page 299, column 1, paragraph 2).

Simon et al. (2000) also notes that the precise molecular mechanisms responsible for leukocyte recruitment to mechanically injured arteries that are devoid of endothelium and the result effects of inflammation on vascular repair after PTCA are unknown (see page 293, column 1, of the Introduction).

(c) There are Numerous Protein Therapies.

Appellant relies upon **Topol et al., JAMA 278: 479-484 (1997)** (Exhibit) for the position that many pharmaceutical proteins and numerous antibodies are administered to patients as therapeutics, absent side effects and without loss of function.

It is not clear where such a holding by **Topol et al.** is indicated.

More importantly, **Topol et al.** states: “A large number of pharmacological agents have failed to reduce restenosis or improve long-term clinical outcomes and the only large-scale trial that reported an effect was the 23% reduction in clinical recurrence at 6 months using abciximab, a monoclonal antibody against the $\beta 3$ integrin” (see page 479, far right column, paragraph 1).

Therefore, **Topol et al.** stands for both
the rejection under 35 USC 112, first paragraph, enablement, in that “a large number of pharmacological agents have failed to reduce restenosis” as well as
the rejection under prior art in that the abciximab is the prior art 7E3 / Reopro antibody that binds GPIIb/IIIa and cross-reacts with Mac-1 and $\alpha v \beta 3$ for the reasons of record.

Appellant remains inconsistent in their position in relying upon **Topol et al.** to stand for enabling the broad scope of “compounds” to treat restenosis, yet the one agent cited by Topol et al. (abciximab, 7E3 antibody) which is employed in the prior art rejections herein is considered non-enabled by appellant. See appellant’s responses to the prior art rejections to **Simon et al. (1995)**, **Genetta et al.** and **Coller et al.**

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Of course, appellant does not mention the high degree of failure of protein, antibody and nucleic acid regulator based therapies in clinical studies and the far greater degree of failure of candidate molecules during drug discovery and development.

As indicated above in the rejection under 35 USC 112, first paragraph, the art as well as the instant **specification** (page 2, paragraph 2) acknowledge the failure of pharmaceutical drugs to treat restenosis.

(d) Summary

Appellant asserts that the examiner has provided mere assumption, not specific support, for alleging that the application is non-enabling.

In contrast to appellant's position, the rejection of record is replete with references supporting the lack of predictability of pharmacological agents in the treatment of restenosis, including the reliance upon numerous types of agents and numerous experimental models leading up to the treatment of restenosis in patients undergoing the claimed cardiovascular surgeries or procedures.

Further, the rejection of record is consistent with appellant's admission concerning the failure of pharmaceutical drugs in the treatment of restenosis at the time the specification was filed.

Here, appellant acknowledged the differences between the attempts to go from the experimental models to the achieving clinical success in stating: "No pharmacologic agent has yet been shown to reduce restenosis in humans" (see page 2, paragraph 2 of the instant **specification**).

More importantly, the rejection has been made particularly in response to the scope of "compounds" and appellant's limited disclosure to support the breadth of compounds employed in the claimed methods.

Appellant is relying upon certain biological activities and the disclosure of a limited representative number of species such as anti-Mac-1 antibodies in an experimental model to support an entire genus of diverse and structurally unrelated compounds targeting a diverse adhesion molecules ligand-receptor molecules, interactions and functions. The instant invention encompasses any "compound which

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specifically reduces or inhibits leukocyte integrin-mediated adhesion or function” that results in the desired reduction or inhibition of stenosis or restenosis”, yet the instant specification does not provide sufficient guidance and direction as to the structural features of said “compounds” and the correlation between the chemical structure and the desired binding and inhibitory function. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biological or pharmacological activities. Therefore, structurally unrelated binding antagonists encompassed by the claimed binding “compounds” would have been expected to have greater differences in their activities

The specification describes assays for determining whether a given compound has certain desired characteristics and identifies some broad categories of compounds that might work, this description of screening assays without more precise guidelines amount to little more than a starting point, a direction for further research .

The specification provides for a plan or an invitation for those of skill in the art to experiment practicing the claimed invention but does not provide sufficient guidance or specificity as to how to execute that plan. It provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement in that will enable any person skilled in the art to make and use the invention

One skilled in the art would not know the identity of any non-disclosed compound falling within the scope of the claim and consequently would not be able to make it. An assay for finding a product is not equivalent for making that product. If the skilled artisan cannot make the product, then the skilled artisan cannot use the product.

Further, the possible enablement of only one or a few embodiments (e.g. antibodies that bind and inhibit Mac-1-mediated interactions) does demonstrate with reasonable specificity how to make and use other potential embodiments (peptides, peptidomimetics, molecules, nucleic acid regulators) in an unpredictable art such as inhibiting or reducing stenosis or restenosis in patients in need undergoing cardiovascular surgeries and procedures.

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In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective therapies for inhibiting restenosis and stenosis, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive for the breadth of "compounds" which specifically inhibits or reduces leukocyte-integrin-mediated adhesion that reduce or inhibit stenosis and restenosis in patients undergoing certain cardiovascular surgeries and procedures.

See the rejection under 35 USC 112, first paragraph, enablement above for analysis.

Rejection Under 35 U.S.C. 112, first paragraph, Written Description

Appellant's arguments have been fully considered but are not found convincing essentially for the reasons of record.

(a) The Legal Standard.

The examiner agrees with that position that the legal standard is met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." See Enzo Biochem., Inc. v. Gen-Probe Incorporated 323 F.3d 956 (Fed. Cir. 2002). Also, see Written Description Guidelines.

However, appellant misreads Enzo Biochem, Inc. v. Gen-Probe 285 F.3d 956 (Fed. Cir. 2002) (Enzo II) by relying upon the ability (and the holding) that deposited materials demonstrated possession of the invention in accordance with 112, first paragraph, requirements and ignores University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC 2004) as well as the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001 (also, see MPEP 2163).

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Enzo II ruled that biological deposits with the ATCC depository could be sufficient to meet the written description requirements

Further, Enzo II adopted the USPTO's Written Description Guidelines that a functional description is adequate when it is coupled with a disclosed correlation between the function and a structure that is sufficiently known or disclosed.

Also, it is noted that Enzo II underscored the point that the issue of written description is a fact-intensive, not a rule-intensive inquiry.

Similarly, appellant's reliance upon the ability of vertebrate and mammalian cells to be engineered to express a protein of interest (e.g. erythropoietin) before the Court in Amgen, Inc. v. Hoechst Marion Roussell, Inc. 314 F.3d 1313 (Fed. Cir. 2003) is clearly different from providing written description for a key critical element of the claim, as recited in the instant application (any "compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function").

Rather than being directed to undescribed and previously unknown genetic sequences, Amgen's claims referred to types of cells that could be used to produce recombinant human erythropoietin and the words "vertebrate" and "mammalian" conveyed sufficient identifying information such that a person of ordinary skill in the art could recognize the identity of the members of the genera of vertebrate cells and mammalian cells. Accordingly, the court found Eli Lilly inapplicable and ruled that the description of a process of producing the claimed erythropoietin in two species of vertebrate or mammalian cells constituted adequate written description of the claimed erythropoietin made using any number of the genus of vertebrate cells or the genus of mammalian cells.

While in Enzo II, biological deposits could satisfy written description and in Amgen, the differences between using the various cells was minimal; the differences here in using undescribed compounds based upon screening procedures to inhibit or reduce stenosis or restenosis in patients undergoing certain cardiovascular surgeries and procedures is significant.

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Here, there is no issue of appellant's reliance upon deposited biological materials to support the broad genus of diverse agents encompassing antibodies, peptides, peptidomimetics, nucleic acid regulators and screening assays to support the written description of the claimed subject matter

Not having "compounds" which have been specifically named or mentioned in a sufficient manner that provides sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics, one is left with selection from the myriad of possibilities encompassed by the broad disclosure with insufficient guides indicating or directing that this particular selection should be made rather than any of the many other which could be made or selected.

One of the many problems with laundry list or shotgun patent disclosures is that while they may lead to numbers games about how many compounds can be disclosed by the use of generic formulas or screening assays, they do little to provide the statutory written description required for patent claims to actual inventions.

Conception does not occur unless one has a mental picture of the structure of the chemical or is able to define by its method of preparation, its physical or chemical properties of whatever characteristics sufficiently distinguish it. It is insufficient to define it solely by its principal biological property because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property

When an inventor is unable to envision the detailed constitution of a "compound" so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e. until after the compounds have been isolated.

(B) The Claims Meet the Written Description Requirement

Appellant's reliance upon the detailed description for classes of compounds, including antibodies (pages 9-11), peptides and peptidomimetics (pages 11-13), nucleic acid molecules (pages 16-19) that inhibit or reduce leukocyte compounds.

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Appellant asserts that these compounds all share the common feature that they all bind integrins or their ligands.

First of all, this is not true as the nucleic acid regulators do not work by binding integrins or their ligands directly.

Appellant asserts that these compounds were known and available as of the date of filing.

Appellant asserts that it was not the discovery of these compounds, but their selection and utility that appellant's claim.

If appellant's position is that the claims are drawn to the use of known compounds in the treatment of cardiovascular patients, then it would appear that appellant is admitting that known compounds given to the same targeted patient populations recited in the claims (e.g. undergoing bypass, angioplasty, atherectomy or stenting) would be anticipate the claimed methods. In turn, then it appears that appellant is in agreement with the prior art rejections that administering antibodies that bind and inhibit Mac-1-mediated interactions to patients recited in the instant claims would result in inhibiting or reducing stenosis or restenosis in such patients in need.

However back in the written description context, this assertion is inconsistent with the numerous statements that no drug treats restenosis, including such acknowledgement by appellant in the specification as filed (See above for a more complete analysis under 35 USC 112, first paragraph, written description).

Appellant also acknowledges the differences between the attempts to go from the experimental models to the achieving clinical success in stating: "No pharmacologic agent has yet been shown to reduce restenosis in humans" (see page 2, paragraph 2 of the instant **specification**).

However, appellant relies upon computer assisted drug design wherein one can model drugs and their interactions with the integrins (e.g. see page 15 of the specification).

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While the specification discloses a starting point for screening or testing for compounds that inhibit or reduce leukocyte integrin - ligand interactions, the instant disclosure does not set forth sufficient procedures that will necessarily lead to discovery for such a compound and it does not identify suitable members of compounds such as peptidomimetics, antisense oligonucleotides, nucleic acid regulators, molecules from a complex mixture of random molecules, natural products and synthetic chemical compounds to provide a sufficient number of species to support the claimed genus of "compounds".

The application does no more than describe the desired function of the claimed compounds broadly encompassed by the claimed invention and does not contain sufficient information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention.

The claimed methods depend upon finding "a compound that specifically inhibits or reduces leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or restenosis in patients undergoing cardiovascular surgery and procedures". Without such a compound, the skilled artisan cannot practice the claimed method of treatment. It means little to invent a method if one does not have possession of the compound(s) that is (are) essential to practice the method. Without possession of the compound(s), the claimed endpoints are illusory and there is no meaningful possession of the method.

Appellant has not provided sufficient written description of a "compound which specifically inhibit or reduce leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue" broadly encompassed by the claimed invention.

There is insufficient or no evidence that there is a recognized structure/function relationship between the disclosed anti-Mac-1 antibody antagonists and any others that might be found using the claimed screening methods. Structural identifying characteristics of the genus members are not disclosed, nor is

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there a description of other identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize that appellant was in position of the scope of the claimed invention of "compounds" employed in the claimed methods.

Here, appellant is claiming a genus where practice of the invention requires use of a compound from a genus whose existence has not yet been described to show that appellant was in possession of the claimed genus.

Appellant asserts that one of skill in the art would know of other compounds and how to make and use them as claimed without undue experimentation.

Again, appellant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 1115).

Appellant has been directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. Also, see MPEP 2163.

Rejection Under 35 U.S.C. 102(b) Genetta et al.

Appellant acknowledges that **Genetta et al.** discloses the results of clinical trials using the chimeric 7E3 (abciximab) antibody to reduce the abrupt closure and restenosis associated with angioplasty (PTCA).

However, appellant asserts that **Genetta et al.** not disclose binding of Mac-1 by abciximab nor disclose inhibiting leukocyte adhesion

In contrast to evidentiary observations of **Schwarz, Bendeck, Wu** and **ERASER Investigations**, appellant relies upon **Mickelson et al. (JACC 33: 97-196, 1999)** to stand for the position that abciximab does not bind directly to Mac-1 (see page 101, column 1).

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In addition, appellant further asserts that no evidence has been provided that this indirect binding would “specifically” inhibit or reduce leukocyte integrin-mediated adhesion

In contrast to appellant’s reading of **Mikelson et al.**, the following is noted.

It is noted that **Mikelson et al.** does disclose that when chimeric 7E3 was administered, leukocyte CD11b expression, especially on neutrophils, diminished and remained low for some time (see page 103, column 2, lines 4-8).

Mikelson et al. does disclose that both the 7E3 and chimeric 7E3 antibodies blocked two Mac-1 (CD11b)-dependent adhesive properties, namely adhesion to fibrinogen and adhesion to ICAM-1 (see page 104, column 1, paragraph 1).

With respect to **Bendeck and Wu**, appellant takes the position that no evidence has been provided that inhibiting leukocyte adhesion reduces smooth muscle migration.

This position appears contrary to the art and to appellant’s own specification and own position concerning one of the hallmarks of restenosis concerning leukocyte adhesion, intimal thickening and restenosis. See The Invention and Clarification of Terms above.

More importantly as pointed out above, the evidentiary references clearly provide for the ability of the 7E3 antibody to bind Mac-1 directly and to inhibit Mac-1-mediated interactions and function.

Schwarz et al. describe the binding of abciximab to Mac-1, in particular the I-domain (also called A-domain) of the Mac-1 α subunit (see entire document, including the Abstract, Results and Discussion).

Schwarz et al. provide evidence that the GPIIb/IIIa-blocking antibody fragment abciximab could inhibit the binding of fibrinogen, iC3b and the coagulation factor X to Mac-1 and that the adhesion of the THP-1 cells to immobilized ICAM-1 and to fibrinogen was reduced significantly by abciximab (see entire document, including the Abstract).

In determining the mechanisms of action by which the beneficial treatment with c7E3 (abciximab, ReoPro) has been associated with a reduction in coronary events and the need for revascularization,

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Bendeck et al. and **Wu et al.** teach that the 7E3 antibody can reduce smooth muscle cell migration following vascular injury which resulted in a decrease in intimal size (see entire documents, including Abstracts and Discussions).

Appellant asserts that the **ERASER study** was cited by the examiner to establish that abciximab does not reduce in-stent restenosis.

The **ERASER Investigators** note that potent platelet inhibition with abciximab does not reduce in-stent restenosis in their study (see entire document, including the Abstract). However, the reference notes that these results should not necessarily be extrapolated to balloon angioplasty because the mechanisms of restenosis differ (see page 805, paragraph 1).

As indicated above in the section Invention and Clarification of Terms in the Response to Arguments in response to the examiner's provision of **Fattori** above, appellant notes that while **Fattori (2003)** states that the mechanisms of restenosis differ between balloon and in-stent catheter injuries, both models share the feature of leukocyte integrin-mediated adhesion although to different degrees (see page 256, paragraph 3 of the **Substitute Brief**). Balloon catheter injury causes greater cell adherence than in-stent injury, which is consistent with Example 2 on pages 22-23 of the instant specification.

Again, this issue of distinguishing between balloon and in-stent catheter injuries was raised by appellant in the provision of the post-filing date reference to stand for the proposition that the 7E3 antibody (i.e. abciximab, Reopro) did not inhibit restenosis.

It is noted that **Fattori** does indicate differences between the balloon and in-stent injuries, which would explain the in-stent results observed by the **Eraser Investigators**.

Again, the prior art teachings provide for the use of the 7E3 antibody in patients undergoing balloon angioplasty.

Appellant has not provide objective evidence to indicate that the 7E3 antibody failed to inhibit restenosis in these patients undergoing balloon angioplasty.

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Also, cited by appellant, it was noted that **Topol et al. JAMA 278: 479-484 (1997)**, which notes that a large number of pharmacological agents have failed to reduce restenosis or improve long-term outcomes and the only large-scale trial that reported an effect was the 23% reduction in clinical recurrence at 6 months using abciximab, a monoclonal fragment directed against the $\beta 3$ integrin (see Introduction on page 479).

For examination purposes, it is noted that c7E3, abciximab and ReoPro are all drawn to essentially the same inhibitory anti-GPIIb/IIIa 7E3 antibody which cross-reacts with both $\alpha_v\beta_3$ and Mac-1 and, in turn, has been considered enabled with respect to the instant claims and has been applied in the prior art rejections with respect to **Genetta et al.** as well as **Simon et al.**, and **Coller et al.**

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Also, see Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Thus, the 7E3 antibody used to inhibit complications associated with certain cardiovascular surgeries or procedures, such as coronary angioplasty, anticipate the claimed methods in the absence of a manipulative difference between the prior art methods and the broadest reasonable interpretation of the instant methods.

Furthermore, appellant relies upon **Dietch et al., Arterioscler Thromb Vasc Biol 18: 1730–1737 (1998)** and **Simon et al. (J. Clin. Invest. 105: 293-300 (2000))** to demonstrate that abciximab has no effect on restenosis.

Dietch et al. is a study on the effects on the response to experimental angioplasty and stenting of arteries in cynomologous monkeys with established atherosclerosis (see Abstract and page 1731, column 1, paragraph 1). This is not the same circumstances as treating patients in need undergoing cardiovascular surgeries and procedures, as taught by the prior art or encompassed by the claimed invention.

Dietch et al. note that $\beta 3$ antagonists have successfully reduced neointimal formation after experimental angioplasty in rabbits and hamsters and the individual components of intimal hyperplasia (cell replication, migration and extracellular matrix elaboration) each depend in part on $\beta 3$ integrins (see

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page 1735, column 1, paragraph 1). Here, **Dietch et al.** further notes that inflammation at sites of injury may also be inhibited by c7E3 blockade of the leukocyte Mac-1 integrin, which mediates fibrinogen and intercellular adhesion molecule-1.

Dietch et al. further indicate that the data suggest that the improved outcomes in the EPIC trial may not be due to changes in artery lumen caliber but to other forms of vessel wall passivation (see page 1735, column 1, paragraph 3).

Dietch et al. also states that: "Although the current study suggests that restenosis may not have been reduced in EPIC, the lack of angiography data from that trial leaves this question unanswered (see page 1753, column 2, paragraph 2).

Further, **Dietch et al.** states: "Differences in animal species, method of arterial injury, a lack of preexisting atherosclerosis and the varied anti- β 3 agents used in each study preclude direct comparisons to the results presented herein."

Simon et al., J. Clin. Invest. 105: 293-3000 (2000) describes the role of inflammation in mechanical arterial injury, including Mac-1.

However, **Simon et al. (2000)** also states: "Although our data showing that antibody blockade of Mac-1 or absence of Mac-1 each reduce neointimal thickening after experimental angioplasty or endovascular stent implantation, the relevance of these observations to clinical angioplasty is unknown." See page 299, column 1, paragraph 2).

Simon et al. (2000) also notes that the precise molecular mechanisms responsible for leukocyte recruitment to mechanically injured arteries that are devoid of endothelium and the result effects of inflammation on vascular repair after PTCA are unknown (see page 293, column 1, of the Introduction).

Although this **Genetta et al.** reference (as well as **Coller et al.** below) is silent about the 7E3 antibody binding Mac-1 (or is silent about restenosis in **Coller et al.** as well), it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC

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2001). “{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable.” In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

On this record, it is reasonable to conclude that the same patient is being administered the antibody that binds Mac-1 and inhibits Mac-1-mediated interactions and adhesion by the same mode of administration in the same amount in both the instant claims and the prior art reference. The fact that applicant's claims may recite yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

As indicated above, for examination and appeal purposes, the prior art rejections rely upon the administration of effective amounts of inhibitors of leukocyte integrin-mediated adhesion (e.g. 0.25 mg/kg - 1.0 mg/kg), including antibodies that bind Mac-1 (CD11b/CD18) in patients undergoing angioplasty, atherectomy, endovascular stenting, coronary artery bypass surgery, peripheral bypass surgery or transplantation of cell, tissue or organs. Such cardiovascular patients are experiencing vascular injury and are in need of treatment, including treatment that targets and inhibits inflammatory mediators or cells that contribute to the events that modulate matrix production and cellular proliferation resulting in stenosis and restenosis.

Rejection Under 35 U.S.C. 102(b) Simon et al. (Circulation)

Appellant acknowledges that while Simon reports that 7E3 antibody was effective at reducing “ischemic complications” and clinical restenosis as well as the ability of the 7E3 antibody to cross-react with Mac-1, appellant states that the 7E3 antibody does not inhibit restenosis.

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Somehow, appellant asserts that **Simon** does not report treatment of patients, dosages, times of administration but simply reports in vitro studies that identify the activity of the antibody as cross-reactive with Mac-1 as well as platelet glycoprotein GPIIb/IIIa.

Simon et al. teach that the 7E3 antibody is used to inhibit ischemic complications of coronary angioplasty and clinical restenosis and that this 7E3 antibody cross-reacts with Mac-1 (see Abstract).

Simon et al. teach the Mac-1-dependent adhesion to fibrinogen and ICAM-1 which are abundant in vessels walls and that Mac-1-expressing cells accumulate in restenosis lesions and have the potential to interact with other vascular cells by secreting growth factors and cytokines (see Abstract). Here, Simon et al. notes that the cross-reaction of c7E3 with Mac-1 may play an additional role in inducing passivity of the vessel wall.

Again, appellant's arguments and the examiner's rebuttal concerning the evidentiary references concerning the ability of the 7E3 antibody to bind and inhibit Mac-1-mediated interactions and adhesion as well inhibiting or reducing stenosis or restenosis in treating patients in need undergoing cardiovascular surgeries and procedures is addressed above in the rejection under 35 USC 102(a)(b) **Genetta et al.** in the **Response to Arguments**.

On this record, it is reasonable to conclude that the same patient is being administered the antibody that binds Mac-1 and inhibits Mac-1-mediated interactions and adhesion by the same mode of administration in the same amount in both the instant claims and the prior art reference. The fact that applicant's claims may recite yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Rejection Under 35 U.S.C. 102 Coller'

Appellant's arguments and the examiner's rebuttal concerning the 7E3 taught by **Coller et al.** are addressed above in the rejection under 35 USC 102(a)(b) **Genetta et al.**.

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Appellant maintains that there is no disclosure of the use of the antibody to inhibit or prevent restenosis, nor of inhibiting leukocyte adhesion by interference with integrin binding.

Again, appellant's arguments and the examiner's rebuttal concerning the evidentiary references concerning the ability of the 7E3 antibody to bind and inhibit Mac-1-mediated interactions and adhesion as well inhibiting or reducing stenosis or restenosis in treating patients in need undergoing cardiovascular surgeries and procedures is addressed above in the rejection under 35 USC 102(a)(b) **Genetta et al.** in the **Response to Arguments**.

On this record, it is reasonable to conclude that the same patient is being administered the antibody that binds Mac-1 and inhibits Mac-1-mediated interactions and adhesion by the same mode of administration in the same amount in both the instant claims and the prior art reference. The fact that applicant's claims may recite yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Rejection Under 35 U.S.C. 102(e) Co

Appellant argues that given that **Co et al.** does not disclose the limitations of stenosis and restenosis, the claimed method is not anticipated.

Although the reference is silent about inhibiting restenosis, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). “{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable.” In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

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On this record, it is reasonable to conclude that the same patient is being administered the same active agent by the same mode of administration in the same amount in both the instant claims and the prior art reference. The fact that applicant's claim may recite yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

It is noted that the claimed methods recite "comprising" which leaves the claim open for the inclusion of unspecified ingredients and methods steps even in major amounts. See MPEP 2111.03.

Rejection Under 35 U.S.C. 102(b) Todd

Appellant acknowledges that **Todd et al.** discloses methods of reducing tissue damage occurring at inflammatory sites in hosts experiencing phagocytic-mediated inflammatory conditions, including inflammation from myocardial infarction or ischemia-reperfusion injury and the insertion of balloon catheters in the circulatory systems with CD11b-CD18 (not CD116/CD18) (column 5, lines 49-53).

However, appellant relies upon the lack of disclosure of treating restenosis as the basis of asserting that Todd et al. does not anticipate the claimed methods.

Although the reference is silent about inhibiting restenosis, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable." In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

On this record, it is reasonable to conclude that the same patient is being administered the same active agent by the same mode of administration in the same amount in both the instant claims and the prior art

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reference. The fact that applicant's claims may recite yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Rejection Under 35 U.S.C. 103

Appellant asserts that there is simply no teaching by the references to lead those in the art to what is claimed.

Appellant asserts that the prior art primary references of **Co et al.**, **Todd et al.**, **Simon et al.** as well as the secondary reference **Mazzone et al.** do not describe a single agent or an antibody that inhibits stenosis or restenosis after injury.

Appellant acknowledges that **Ikeda et al.** show Mac-1 as a non-specific marker of leukocyte activation is increased after PTCA. However, appellant asserts that no data has been shown that Mac-1 is involved in restenosis.

Appellant asserts that both **Inoue et al.** and **Rogers et al.** do not disclose an antibody specific to Mac-1.

Appellant asserts that efforts at limiting the undesirable proliferative and disease states of vascular endothelium have focused on the isolated administration of analogs of endothelial compounds to support the position that one skilled in the art would not expect only a single compound to be effective in limiting or preventing restenosis.

As indicated above, **Co et al.** teach methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury in various modalities including cardiac surgery such as coronary artery bypass and elective angioplasty (see entire document, including columns 17-18, overlapping paragraph and column 18, paragraph 3-4) wherein the L-selectin-specific antibodies can be used in combination with other humanized or human antibodies reactive with CD11b (i.e. Mac-1) (column 18, paragraph 1).

As indicated above, **Todd et al.** teach methods of reducing tissue damage occurring at an inflammatory site in a host experiencing a phagocyte-mediated inflammatory conditions, including inflammation from myocardial infarction or ischemia-reperfusion injury and the insertion of balloon

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catheters in the circulatory system with CD11b- / Mac-1- specific antibodies (see entire document, including Claims).

Although these references do not disclose the limitations of stenosis and restenosis per se, these claimed endpoints would be expected, intrinsic or desired endpoints by administering effective amounts of CD11b / Mac-1-specific antibodies in the same patient populations targeted and encompassed by the claimed methods. Given the referenced methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury in various modalities including cardiac surgery such as coronary artery bypass and elective angioplasty, the ordinary artisan would have had an expectation of success that anti-CD11b antibodies would have inhibited or reduced restenosis or stenosis arising from patients undergoing said cardiovascular surgeries and procedures.

In teaching that 7E3 antibody is used to inhibit ischemic complications of coronary angioplasty and clinical restenosis and that this 7E3 antibody cross-reacts with Mac-1;

that the Mac-1-dependent adhesion to fibrinogen and ICAM-1, ligands which are abundant in vessels walls and that Mac-1-expressing cells accumulate in restenosis lesions and have the potential to interact with other vascular cells by secreting growth factors and cytokines; and

that the cross-reactivity of c7E3 with Mac-1 may play an additional role in inducing passivity of the vessel wall;

Simon et al. provided additional motivation and expectation of success in targeting Mac-1 in therapeutic interventions associated with the complications of angioplasty including restenosis at the time the invention was made.

The following references cited above provided further support for targeting Mac-1 in the treatment of complications of angioplasty including restenosis.

Mazzone et al. teach the CD11b/CD18 plays a major role in the leukocyte adhesion process and can be upregulated severalfold in response to chemotactic factors (see Background). Mazzone et al. further teach that patients with unstable angina have an increased expression of granulocyte and monocyte CD11b/CD18, indicating that an inflammatory reaction takes place with their coronary tree. Activation of these leukocytes may induce coronary vasoconstriction, favor thrombotic processes, and further activate platelets, thus having potential implications on the pathogenesis of unstable coronary artery disease (see

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Conclusion). The Discussion provides a teaching of the importance of CD11/CD18 in tissue injury in vivo in a number of animal models, including that the addition of anti-CD18 antibodies can reduce tissue injury and mortality in ischemia reperfusion injury-induced shock and myocardial infarct size (see Discussion on page 360, column 1).

Ikeda et al. teach the surface expression of CD11b of neutrophils increased significantly after percutaneous transluminal coronary angioplasty (PTCA) (see entire document, including Abstract, Results and Discussion). Ikeda et al. teach anti-CD11b antibody inhibits several neutrophil functions, including the binding of C3bi-opsonized particles, adhesive interactions of neutrophils, spreading on vascular endothelium and chemotaxis (see Discussion, particularly page 1095, column 2). Ikeda et al. further teach that anti-CD11b antibodies significantly reduced neutrophil accumulation within the infarct area (see Discussion, particularly page 1095, column 2). With respect to restenosis, Ikeda et al. teach that neutrophil activation after PTCA in humans appears to play an important role in the initial step of inflammatory phase and then to trigger the pathophysiologic chain reaction eventually resulting in coronary restenosis (see Clinical Implications on page 1096-1097). Ikeda et al. note here that activated neutrophils can potentiate platelet activity, in turn, leading to vasoconstriction and proliferation of vascular smooth muscle.

Inoue et al. teach inflammatory stimuli within the coronary vessels associated with coronary angioplasty upregulate Mac-1 expression on the surface of PMNs and this process is more marked in patients who experience later restenosis (see entire document, including Conclusions). The activation of neutrophil adhesion molecule after PTCA has valued as a predictor of subsequent restenosis (see Conclusion). Inoue et al. teach that the same cytokines that stimulate the expression of leukocyte adhesion molecules, such as Mac-1 also stimulate smooth muscle cell proliferation.

Rogers et al. teach that the inhibition of neointimal hyperplasia and thrombosis depends on the type of vascular injury and the site of drug administration (see entire document, including Abstract and Discussion). Here, Rogers et al. teach different forms of injury may require different therapeutics and complication of arterial intervention such as excessive neointimal hyperplasia and thrombosis may demand alternative therapeutic regimens. Duration, dose, and site of delivery rather than frank resistance to therapy may explain why experimental effective antiproliferative and antithrombotic agents fail clinically.

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Appellant submits that this demonstrated by **Co et al.** where antibodies are administered in combination with thrombolytic agents or angioplasty.

Appellant is reminded that the claims recite "comprising and do not exclude unrecited ingredients or method steps. Further, such thrombolytic agents or procedures such as angioplasty were employed in therapeutic regimens associated with the patients targeted by the prior art and the claimed invention.

Although certain references do not disclose the targeted endpoint of reducing or inhibiting stenosis or restenosis per se, it was clear that the references do teach targeting Mac-1 with effective amounts encompassed by the claimed invention (e.g. 0.25 mg/kg or more in single or multiple doses) in order to inhibit various inflammatory consequences of Mac-1 expressing cells in therapeutic regimens associated with stenosis or restenosis such as angioplasty or bypass surgery. In addition, the combined references do teach targeting either stenosis, restenosis or endpoints associated with stenosis or restenosis (occlusion, intimal hyperplasia). The claimed methods comprises the same steps, the same effective amounts and the same targeted patient populations as the prior art. In addition, **Rogers et al.** teach duration, dose, and site of delivery are important in achieving therapeutic endpoints aimed at limiting restenosis such as inhibiting intimal hyperplasia (see entire document). Given the well known complications of stenosis and restenosis associated with various procedures such as angioplasty or bypass surgery at the time the invention was made, one of ordinary skill in the art would have had an expectation of success that treating these conditions or procedures with effective amounts of anti-Mac-1 antibodies would have resulted in the inhibition or reduction of certain endpoints associated with stenosis or restenosis arising in patients undergoing certain cardiovascular surgeries and procedures.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Appellant's arguments are not found persuasive.

Once again during the prosecution of this application, appellant has cited references, now including **Edelman et al. Circ. 89: 770-776 (1994), Cooke et al., Curr. Opin. Cardiol 7: 799-804 (1992),**

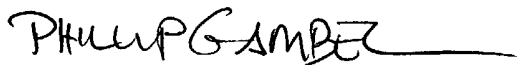
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Moncada et al., N. Eng. J. Med. 329 : 2002-2012 (1993) and McNamara et al., Biochem. Biophys. Res. Comm. 193: 291-296 (1993), which appellant has not provided.

Theses references have not been considered by the examiner.

(12) For the above reasons, it is believed that the rejection should be sustained.

Respectively submitted,



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December 6, 2004


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